THE SCIENCE AND PRACTICE OF PEDIATRIC CARDIOLOGY

volume II

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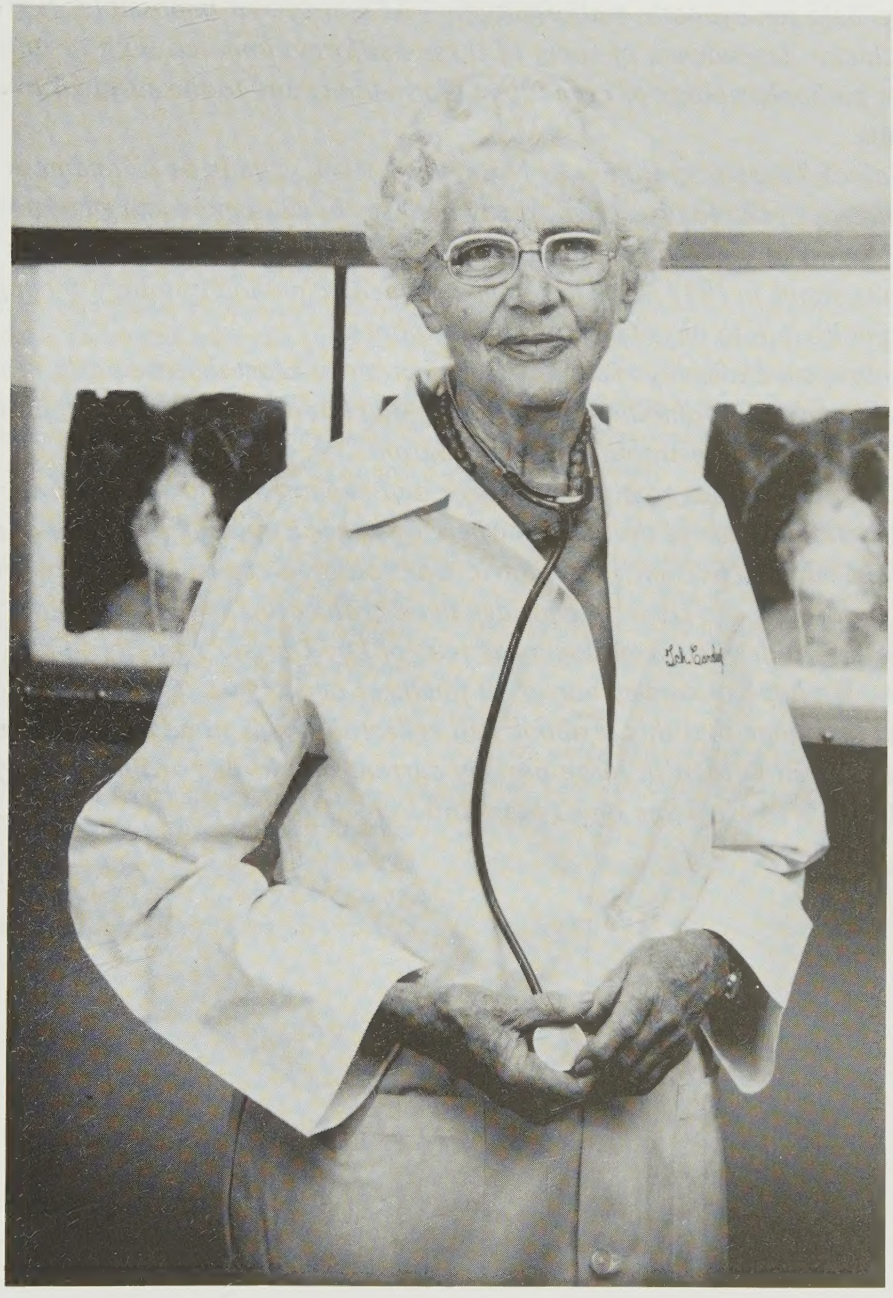

Dr. Helen Brooke Taussig in the Conference Room named after her in Texas Children's Hospital.

Dr. Helen Taussig had a profound influence on the professional lives of most of the authors of this book as well as on the personal life of many of us. She visited this medical center often, lecturing, consulting on patients, and having informal conversations with the students and house staff. Because of her warm manner and directness, and her intense concern for other people, she acquired devoted friends and disciples among physicians and laymen all over the world.

We acknowledge her many contributions to science and to clinical medicine, but it is her gift to us as a marvelous human being that prompts us to dedicate this work to her.

Dr. Taussig stands as the acknowledged founder of Pediatric Cardiology. In the era when definitive help for cyanotic malformations was considered impossible, her observation of the ductal dependence of some of these malformations led both to an understanding of the pathophysiology of cyanotic malformations and to the surgical treatment of these patients.

The first Blalock-Taussig operation in November, 1944, stands as a landmark in the history of Pediatric Cardiology and led, many believe, to subsequent surgical treatment of virtually all forms of both congenital and acquired heart diseases. Publication of her clearly written textbook in 1947 made the often complicated pathophysiology of congenital heart defects intelligible to physicians of all disciplines.

Dr. Taussig proposed altering risk factors for coronary heart disease early in life for all children; an innovative if ambitious undertaking that has not yet been widely practiced, although many accept the desirability of the program.

One of her many activities was to encourage and support her former fellows. Texas Children's Hospital was one of the centers where a former trainee of Dr. Taussig's (Dan McNamara) headed the Division of Pediatric Cardiology. Because she considered her fellows her "children," she came to consider those trained by her fellows her "grandchildren." Texas Children's Cardiology was part of Dr. Taussig's family, and we miss her very much. We hope to convey our great fondness and respect for Dr. Taussig with this dedication and hope that this textbook will reflect the high standards she taught.

This book has been written in large part by current and former trainees and faculty from Baylor College of Medicine and Texas Children's Hospital.

Preface

The clinical practice of Pediatric Cardiology started in the early 1930's–1940's when pioneers in the yet unborn specialty were beginning to sort out the mysteries of congenital malformations. They started to put together those pieces of the puzzle that were available at the time, namely the electrocardiogram (limb leads only), the radiographic (especially the fluoroscopic) image of the heart, the physical examination, and with a limited yield, the "history." There was the all too inevitable opportunity to check the manifestations of the anomalies against the later autopsy findings.

The late Dr. Helen Taussig, to whom this work is dedicated, was a master at this. She remarked that, while there was no specific treatment for the patients during the early years, she sensed that these efforts at specific diagnosis were surprisingly comforting to the parents. When it became essential to distinguish one cyanotic malformation from another in order to select the correct operation, cardiac catheterization and angiocardiography became practical tools and Pediatric Cardiology developed precipitantly.

The clinical practice of Pediatric Cardiology preceded by many years the body of scientific knowledge pertinent to the field which was uncovered by research. Much of what had been learned in the clinical area was largely on the basis of deductive reasoning, but that approach had carried Pediatric Cardiology up to only a certain limit. Basic research promoted the unravelling of the scientific basis of the discipline, and this in turn advanced the clinical management of the patient.

These volumes seek to present what is known today about the preferred methods of management of the patient as well as the scientific foundation for these methods. The basic science of Pediatric Cardiology is beginning to catch up and appropriately lead the way to improved patient care and to prevention of some forms of heart disease.

The Sub-Board of Pediatric Cardiology, recognizing the needed exchange between science and practice, urges—indeed demands—that training programs include basic science courses in their curriculum, the teaching of research methods to trainees, and hands on experience in the laboratory working with an active and productive investigator. Thus, it seems timely that a text devoted to the practice and science of Pediatric Cardiology make its appearance now.

We would like to express our sincere appreciation to our assistants, Candy Liedtke, Paulette Snowden, and Steven Neish, M.D. without whom the task would have been insurmountable.

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Contents

Volume I

UNIT 1
BASIC SCIENCE TOPICS PERTINENT TO THE CARDIOVASCULAR SYSTEM THROUGHOUT DEVELOPMENT

1. *Molecular Genetics of the Cardiovascular System* ... 3
   JEFFREY A TOWBIN
   ROBERT R ROBERTS
   C THOMAS CASKEY
2. *Cardiac Embryology* ... 71
   EDWARD V COLVIN
3. *Cardiovascular Anatomy* ... 109
   JACK L TITUS
   DEBRA L KEARNEY
4. *Epidemiology* ... 135
   DARWIN A LABARTHE
   CLAUDIA KOSINETZ
   THOMAS McINTOSH JONES
5. *Experimental Embryology and Teratology* ... 152
   TIM C McQUINN
   ATSUYOSHI TAKAO
6. *Chromosomal Abnormalities and Heritable Aspects of Pediatric Cardiology* ... 171
   FRANK GREENBERG
7. *Cardiac Metabolism* ... 191
   G WESLEY VICK, III
   DAVID J FISHER
8. *Excitation—Contraction Coupling: Control of Normal Myocardial Cellular Calcium Movements* ... 202
   CHARLOTTE A TATE
   GEORGE E TAFFET
   DAVID J FISHER
9. *Cardiac Contractile Proteins in the Normal Heart: The Contractile Process and Its Regulation* ... 212
   LLOYD H MICHAEL
10. *Indices of Myocardial Contractility* ... 223
    DAVID J FISHER
    DAVID C MAYER
11. *Regulation of Cardiac Pump Function* ... 231
    WILLIAM J DREYER
    DAVID J FISHER
12. *Mechanisms of Congestive Cardiac Failure* ... 244
    MARTIN P O'LAUGHLIN
    DAVID J FISHER
13. *Regulation of Myocardial Blood Flow and Oxygen Consumption* ... 250
    STEPHEN M PARIDON
    DAVID J FISHER
14. *Pathogenesis of Ischemic Myocardial Injury and Methods for Myocardial Protection* ... 266
    BHARAT PATEL
    MOHAMMED O JEROUDI
    ROBERTO BOLLI
15. *Fetal Circulation and Changes Occurring at Birth* ... 280
    ALFRED L GEST
    ALICIA A MOÏSE
16. *The Regulation of Systemic Oxygen Delivery* ... 289
    VICTORIA E JUDD
    DAVID J FISHER
17. *Cardiac Electrophysiology* ... 294
    JEFFREY P MOAK
18. *Cardiovascular Receptors* ... 318
    JULIUS C ALLEN
19. *Interaction of the Nervous System and the Heart* ... 325
    ADDISON A TAYLOR
    BARRY MARCUS
20. *Basic Pulmonary Anatomy and Physiology* ... 349
    OTWELL D TIMMONS
    LARRY S JEFFERSON
21. *The Pulmonary Circulation* ... 360
    ROMA L ILKIW
    WANDA C MILLER-HANCE
    MICHAEL R NIHILL
22. *Pulmonary Edema* ... 386
    TIMOTHY F FELTES
    THOMAS N HANSEN
23. *Cardiopulmonary Resuscitation* ... 401
    LARRY S JEFFERSON
    THOMAS C MAYES

24. *The Physiology of Exercise in Children* ... 428
ILEY W BROWNING
J TIMOTHY BRICKER

25. *Cardiovascular Developmental Physiology at Zero Gravity: A Baby in Space* ... 435
WILLIAM E THORNTON

26. *Altitude Physiology* ... 441
MARK C DUSTER

27. *Renal Physiology* ... 450
L LEIGHTON HILL

28. *Principles of Clinical Pharmacology* ... 468
JEFFREY P MOAK

29. *Lipid Metabolism and Atherogenesis* ... 475
JOHN R GUYTON

30. *Basic Science of Blood Pressure Measurement* ... 492
YADIN DAVID

31. *Basic Science of Blood Flow Measurement* ... 494
NIELS G GIDDINS
DAVID J FISHER

32. *Basic Science Aspects of the Electrocardiogram* ... 500
ANNE FOURNIER

33. *Basic Science Aspects and Technical Considerations of Echocardiographic Imaging* ... 524
DAVID A DANFORD

34. *Basic Science Aspects of Doppler Echocardiography* ... 534
DANIEL J MURPHY, JR

35. *Basic Aspects of Instrumentation, Radiation, and Facilities* ... 542
YADIN DAVID

36. *Basic Science Aspects of Nuclear Cardiology* ... 559
HENRY B WILES

37. *Nuclear Magnetic Resonance and Positron Emission Tomography—Basic Science Aspects* ... 570
G WESLEY VICK, III
ROXANN ROKEY
DONALD L JOHNSTON

38. *Basic Science Aspects of Computed Tomography* ... 628
BARRY D TOOMBS

39. *Basic Science Aspects of Digital Subtraction Angiography* ... 635
WILLIAM W PINSKY
KARL KELLAR

40. *Research Design* ... 642
DAVID J FISHER

41. *Statistics for the Cardiologist* ... 646
J TIMOTHY BRICKER
DAVID J FISHER
ARTHUR GARSON, JR

42. *Computers in Cardiology* ... 656
G WESLEY VICK, III
MICHAEL R NIHILL
DAVID J FISHER

Volume II

UNIT 2
NONINVASIVE DIAGNOSTIC METHODS

43. *History and Physical Examination of the Cardiovascular System* ... 671
DESMOND F DUFF
DAN G MCNAMARA

44. *Noninvasive Diagnostic Methods: Plain Radiographic Diagnosis of Congenital Heart Disease* ... 691
EDWARD B SINGLETON
MARY J H MORRISS

45. *Electrocardiography* ... 713
ARTHUR GARSON, JR

46. *Echocardiography, Two-Dimensional and M-Mode* ... 768
JAMES C HUHTA

47. *Doppler Echocardiography* ... 784
DANIEL J MURPHY, JR

48. *Fetal Echocardiography* ... 805
W ROBERT MORROW
JAMES C HUHTA

49. *Exercise Testing* ... 828
FRANK M GALIOTO, JR

50. *Nuclear Cardiology* ... 836
HENRY B WILES

51. *Nuclear Magnetic Resonance and Positron Emission Tomography—Clinical Aspects* ... 852
G WESLEY VICK, III
ROXANN ROKEY
DONALD L JOHNSTON

52. *Computed Tomography* ... 880
BARRY D TOOMBS

UNIT 3
INVASIVE DIAGNOSTIC METHODS

53. *Digital Subtraction Angiography* ... 907
WILLIAM W PINSKY
DAVID W JONES

54. *Cardiac Catheterization—Hemodynamic Measurements* ... 913
THOMAS A VARGO

55. *Catheterization and Angiography* ... 946
MICHAEL R NIHILL

56. *Selective Coronary Arteriography in Children with Heart Disease* ... 968
G ALI MASSUMI
ROBERT J HALL

57. *Peripheral Vascular Angiography* ... 973
MARK D SKOLKIN

UNIT 4
STRUCTURAL CONGENITAL CARDIOVASCULAR DEFECTS

58. *Clinical Physiology of Left-to-Right Shunts* ... 999
MADELINE S MAS
J TIMOTHY BRICKER

59. *Ventricular Septal Defect* ... 1002
CARL H GUMBINER
ATSUYOSHI TAKAO

60. *Defects of the Atrial Septum Including the Atrioventricular Canal* ... 1023
G WESLEY VICK, III
JACK L TITUS

61. *Patent Ductus Arteriosus* ... 1055
CHARLES E MULLINS

62. *Clinical Physiology of Right-to-Left Shunts* ... 1070
J TIMOTHY BRICKER

63. *Tetralogy of Fallot and Tetralogy of Fallot with Pulmonary Atresia* ... 1073
WILLIAM H NECHES
SANG C PARK
JOSE A ETTEDGUI

64. *Absent Pulmonary Valve Syndrome* ... 1101
WILLIAM W PINSKY

65. *Pulmonary Valve Atresia with Intact Ventricular Septum* ... 1108
DONALD A RIOPEL

66. *Tricuspid Atresia* ... 1118
DAVID J DRISCOLL

67. *Truncus Arteriosus* ... 1127
ROBERT L WILLIAMS
ROBERT J SOMMERVILLE

68. *Ebstein's Anomaly of the Tricuspid Valve* ... 1134
CO-BURN J PORTER

69. *Anomalous Pulmonary Venous Connections; Pulmonary Vein Stenosis; Atresia of the Common Pulmonary Vein* ... 1145
KENT A WARD
CHARLES E MULLINS

70. *Transposition Physiology* ... 1173
J TIMOTHY BRICKER

71. *Transposition of the Great Arteries* ... 1175
WILLIAM H NECHES
SANG C PARK
JOSE A ETTEDGUI

72. *Double-Outlet Ventricles* ... 1213
MICHAEL J SILKA

73. *Ventricular Inversion* ... 1233
CHARLES E MULLINS

74. *Single Ventricle* ... 1246
EDWARD V COLVIN

75. *Cardiac Malposition and Heterotaxy* ... 1280
HOWARD P GUTGESELL

76. *Clinical Physiology of Obstructive and Regurgitant Lesions* ... 1304
KENNETH O SCHOWENGERDT, JR
J TIMOTHY BRICKER

77. *Cor Triatriatum, Pulmonary Vein Obstruction, Supravalvar Mitral Stenosis, and Congenital Mitral Valve Disease* ... 1308
JANETTE F STRASBURGER

78. *Hypoplastic Left Heart Syndrome* ... 1316
GERALD BARBER

79. *Aortic Stenosis: Valvular, Supravalvular, and Fibromuscular Subvalvular* ... 1334
LARRY A LATSON

80. *Coarctation of the Aorta and Interrupted Aortic Arch* ... 1353
MARY J H MORRISS
DAN G McNAMARA

81. *Pulmonary Stenosis* ... 1382
JOHN P CHEATHAM

82. *Aortic Arch and Pulmonary Artery Anomalies* ... 1421
W ROBERT MORROW
JAMES C HUHTA

83. *Congenital Coronary Artery Anomalies* ... 1453
DAVID J DRISCOLL

84. *Anomalies of Systemic Venous Return* ... 1462
JAMES C HUHTA

85. *Arteriovenous Fistulae* ... 1471
L PAUL GERSON

UNIT 5
INFLAMMATORY CARDIOVASCULAR DISEASE

86. *Acute Rheumatic Fever* ... 1485
GALAL M EL-SAID
KHALID A SOROUR

87. *Rheumatic Heart Disease* ... 1502
GALAL M EL-SAID
MEDHAT M EL-REFAEE

88. *Cardiovascular Manifestations of Connective Tissue Diseases* ... 1527
KARYL S BARRON

89. *Kawasaki Disease* ... 1542
JUNICHIRO FUKUSHIGE
MICHAEL R NIHILL

90. *Infective Endocarditis* ... 1561
RICHARD A FRIEDMAN
JEFFREY R STARKE

91. *Myocarditis* ... 1577
RICHARD A FRIEDMAN

92. *Pericarditis* ... 1590
WILLIAM W PINSKY
RICHARD A FRIEDMAN

93. *Postoperative Inflammatory Syndromes* ... 1600
SANDRA K CLAPP

94. *Pediatric Acquired Immune Deficiency Syndrome* ... 1605
I CELINE GUERRA HANSON
WILLIAM T SHEARER

Volume III

UNIT 6
MYOCARDIAL DISEASE

95. *Cardiomyopathy* ... 1617
MARC PAQUET
BRIAN D HANNA

96. *Cardiac Tumors* ... 1647
ACHI LUDOMIRSKY

97. *Metabolic Heart Disease* ... 1656
BRUCE D GELB

98. *Myocardial Infarction in Childhood* ... 1684
JEFFREY A TOWBIN

UNIT 7
ARRHYTHMIAS

99. *Noninvasive Arrhythmia Diagnosis* ... 1725
PETER S HESSLEIN

100. *Electrophysiology Studies* ... 1743
PAUL C GILLETTE
BERTRAND A ROSS
VICKI ZEIGLER
DAVID BUCKLES
MARK HAROLD

101. *Sinus Node Dysfunction* ... 1751
JOHN D KUGLER

102. *Bundle Branch Block* ... 1786
MICHAEL J SILKA

103. *Atrioventricular Block* ... 1800
BERTRAND A ROSS

104. *Supraventricular Tachycardia* ... 1809
ACHI LUDOMIRSKY
ARTHUR GARSON, JR

105. *Atrial Flutter and Atrial Fibrillation* ... 1849
CO-BURN J PORTER

106. *Ventricular Arrhythmias* ... 1864
ARTHUR GARSON, JR

107. *Fetal Arrhythmias* ... 1905
JANETTE F STRASBURGER

108. *Sudden Cardiac Death in Children* ... 1912
PAUL C GILLETTE
BERTRAND A ROSS
VICKI ZEIGLER

UNIT 8
OFFICE PEDIATRIC CARDIOLOGY

109. *Innocent Murmurs and Heart Sounds* ... 1919
DAVID A DANFORD
DAN G McNAMARA

110. *Syncope* ... 1929
MARTIN P O'LAUGHLIN
DAN G McNAMARA

111. *Chest Pain* ... 1947
MARK C DUSTER

112. *Irregular Heart Beat* ... 1951
JOES R JACOBSEN
ARTHUR GARSON, JR

113. *Infants with Congenital Heart Disease in the First Year of Life* ... 1959
DAVID A DANFORD
DAN G McNAMARA

114. *Mitral Valve Prolapse* ... 1973
VICTORIA EVANS JUDD

115. *Systemic Hypertension and Preventive Cardiology* ... 1987
J TIMOTHY BRICKER
SARAH D BLUMENSCHEIN

116. *Consequences of Chronic Hypoxemia and Pulmonary Vascular Disease* ... 1996
STEPHEN M PARIDON

117. *Congestive Heart Failure* ... 2007
WILLIAM J DREYER

118. *Residua, Sequelae, and Complications of Heart Surgery* ... 2024
MARY J H MORRISS
DAN G McNAMARA

UNIT 9
THERAPEUTICS

119. *Antimicrobial Therapy* ... 2047
SHELDON L KAPLAN
MARK W KLINE

120. *Inotropic Agents* ... 2065
TIMOTHY F FELTES

121. *Anticoagulant and Thrombolytic Agents* ... 2079
C PHILIP STEUBER

122. *Afterload Manipulation* ... 2086
JOHN W MOORE

123. *Diuretic Therapy* ... 2099
BARRY MARCUS

124. *Medical Manipulation of the Ductus Arteriosus* ... 2108
ANTHONY J CORBET

125. *Antiarrhythmic Drugs* ... 2126
JANETTE F STRASBURGER

126. *Pacemakers for Bradycardia* ... 2135
RICHARD T SMITH, JR

127. *Antitachycardia Pacing* ... 2156
PAUL C GILLETTE
BERTRAND A ROSS
VICKI ZEIGLER

128. *Electrical Treatment of Arrhythmias* ... 2162
JEFFREY P MOAK

129. *Surgical Treatment for Disturbances of Cardiac Rhythm* ... 2174
DAVID A OTT

130. *Therapeutic Cardiac Catheterization* ... 2183
CHARLES E MULLINS

131. *Decisions and Techniques in Congenital Heart Surgery* ... 2210
DAVID A OTT
DENTON A COOLEY

132. *Pediatric Cardiac Transplantation* ... 2227
O HOWARD FRAZIER
MICHAEL P MACRIS

133. *Immunologic Aspects of Heart Transplantation: Rejection, Immunosuppression, Infection, and Malignancy* ... 2239
I CELINE GUERRA HANSON
O HOWARD FRAZIER
WILLIAM T SHEARER

134. *Postoperative Care* ... 2251
TIMOTHY J BELL

135. *Cardiac Rehabilitation for Children* ... 2267
FRANK M GALIOTO, JR

UNIT 10
SPECIALTY KNOWLEDGE FOR THE PEDIATRIC CARDIOLOGY CONSULTANT

136. *Acquired Coronary Artery Disease* ... 2277
ROBERT D LEACHMAN

137. *Anesthesia and Cardiopulmonary Bypass* ... 2289
JOHN R COOPER
ARTHUR S KEATS

138. *Neurologic Issues of Importance for the Pediatric Cardiologist* ... 2305
MARVIN A FISHMAN
JULIE T PARKE

139. *Hematologic Issues of Importance for the Pediatric Cardiologist* ... 2328
DONALD H MAHONEY, JR
KENNETH L McCLAIN
ZOANN E DREYER

140. *Dentistry* ... 2350
V KAYRON DUBE

141. *Nutrition, Growth, and the Gastrointestinal System: Basic Knowledge for the Pediatric Cardiologist* ... 2354
MARK GILGER
CRAIG JENSEN
BRADLEY KESSLER
PRATHIBA NANJUNDIAH
WILLIAM J KLISH

142. *Contraception for the Pediatric Cardiology Patient* ... 2371
SUSAN F POKORNY

143. *Pregnancy and Cardiovascular Disease* ... 2374
PATRICK F GLASOW
ROBERT J CARPENTER, JR

144. *Genetic Syndromes* ... 2397
FRANK GREENBERG
ARNOLD J RUDOLPH

145. *Cutaneous Manifestations of Cardiac Disease* ... 2414
MOISE L LEVY
PERRY J SCALLAN

146. *Nephrology for the Pediatric Cardiologist* ... 2425
PHILLIP L BERRY

147. *Orthopedic Considerations for the Pediatric Cardiologist* ... 2445
DOUGLAS A BARNES

148. *Infections and Immunizations* ... 2462
SHELDON L KAPLAN
CHRISTIAN C PATRICK

149. *Neonatology* ... 2477
JAMES M ADAMS

150. *Endocrinology: Considerations for the Pediatric Cardiologist* ... 2491
DOUGLAS G ROGERS

151. *Pulmonology: Considerations for the Pediatric Cardiologist* ... 2501
DEBRA A PARRISH
DAN K SEILHEIMER

152. *Psychological Aspects of Heart Disease in Childhood* ... 2519
SUZAN L GARSON
PAUL E BAER

153. *Employability and Insurance* ... 2528
JOAN E SHOOK

154. *Cardiac Trauma* ... 2534
STEVEN R NEISH

Appendixes ... 2541
JAMES C PERRY

Appendix I *Management of Cardiac Emergencies* ... 2541

Appendix II *Drug Formulary* ... 2548

Appendix III *Miscellaneous* ... 2555

Index ... i

UNIT 2

NONINVASIVE DIAGNOSTIC METHODS

CHAPTER 43

History and Physical Examination of the Cardiovascular System

Desmond F Duff
Dan G McNamara

Despite major advances in noninvasive diagnosis, especially cardiac ultrasound, the history and physical examination remain important as a screening method in first the detection of heart disease in infants and children and then the evaluation of its severity.

There are a few congenital malformations in which the anatomical defect can be defined with a high degree of accuracy by physical examination alone. Usually, however, precise diagnosis requires graphic studies, ultrasound imaging, and often cardiac catheterization and angiocardiography.

Since the majority of patients who have critical congenital heart disease present during the first year and especially in the first few weeks of life, the first part of this chapter emphasizes the role of the history and physical examination in that age group.

The term "disease" is used in this chapter to indicate any departure from normal and includes congenital malformations as well as acquired or infectious or degenerative processes. "Disease" may also denote functionally benign departures from normal as well as important or life-threatening pathologic conditions.

In a prospective longterm followup study, Hoffman and Christianson[1] reported that, for subjects with congenital heart disease, the diagnosis was made in 46% by the age of 1 week and in 88.3% by the age of 1 year; 98.8% were diagnosed by 4 years of age. The diagnoses were made or confirmed at autopsy in 39 subjects (23.9%), at operation in 23 (14.1%), after cardiac catheterization in 17 (10.4%), and from clinical examination alone in 84 (51.5%). When examining a newborn infant, it is helpful to keep in mind that about one third of the infants who subsequently prove to have important congenital heart disease may be discharged as apparently well from maternity hospitals.[2]

Congenital heart disease is the single most common major congenital anomaly; it is responsible for 3 to 5% of deaths during the first week of life and up to 33% of deaths during the entire neonatal period.[3] In addition, twice as many infants die in the first month of life as die after 1 year of age from this cause.[4]

IDENTIFICATION OF FUNCTIONALLY IMPORTANT HEART DISEASE IN INFANTS AND CHILDREN

Symptoms that may be associated with congenital heart disease in a small infant include the obvious ones such as cyanosis, tachypnea, and labored breathing. In addition, such infants may have feeding difficulties, failure to gain weight adequately, sweating, irritability, or lethargy.

In childhood, the patient may be able to verbalize complaints such as shortness of breath with exercise, fatigue, dizziness, or palpitations. Delay of sexual maturation may be a sign of serious interference with cardiac output in pubertal-age patients.

Cyanosis

Cyanosis (Greek: "kuanosis" = blueness) is a blue discoloration of the skin caused by the presence of deoxygenated blood within the capillary network. Lundsgaard and Van Slyke[5] stated in 1923 that cyanosis was due to the presence of 4 to 6 g or more of reduced hemoglobin in capillary blood. Cyanosis may be either peripheral or central.

The term "cyanosis," unspecified, simply means a blue color of the skin, mucous membranes, or nailbeds. In taking a history, physicians sometime disregard the fact that there are reasons other

than arterial oxygen desaturation for a bluish appearance of the skin or mucous membranes. The parents of a healthy individual might report quite accurately that their child does turn blue at times. The history taker might automatically interpret this to indicate hypoxemia, while the mechanism could be the benign phenomenon of acrocyanosis. This can result from unusual but nevertheless physiologic prominence of diffuse veins around the eyes, nose, or lips, especially in fair or blond children. The blue color could represent the phenomenon of intermittent vasomotor changes in the skin, cutis marmorata, which is a pink, marble-like mottling of the skin that appears on exposure to a cold environment and is common in children and some adults. Cutis marmorata is presumably caused by cutaneous small arterial constriction leaving visible small cutaneous blue venules. Ordinarily, these venules are obscured by a fully filled plexus of small cutaneous arteries giving the normal pink color to the skin. This phenomenon might be brought on in certain susceptible but healthy individuals by exposure to cold ambient temperature or immersion in chilly water.

A pathologic cause of acrocyanosis is the mechanism of cutaneous arterial constriction resulting from low cardiac output. Cutaneous arterial constriction is one of the body's mechanisms to conserve blood flow for the protection of vital organs. Cretins with reduced cardiac output typically manifest this phenomenon.

Individuals with low cardiac output and pulmonary edema may exhibit cyanosis that is related to both hypoxemia caused by ventilatory insufficiency and acrocyanosis caused by lowered cardiac output.

So-called "central" cyanosis is evident when there are 3 g or more of reduced hemoglobin in the arterial blood and the blueness is noted in the mucous membranes and tongue as well as in the nailbeds of the extremities, which are usually warm (rather than cold as in acrocyanosis).[6] Central cyanosis, which implies arterial blood oxygen desaturation, is caused by an intracardiac or intrapulmonary right-to-left shunt.

Central cyanosis may be physiologic up to 20 minutes after birth; however, beyond that time, it is almost always a manifestation of serious cardiac or respiratory disease.[6,7] In order for the lips and nailbeds to appear actually blue, the arterial blood oxygen saturation must be quite low, in the range of 60 to 70%. If there is polycythemia, then blueness can be detected by physicians at a higher level of saturation. A clinically detectable abnormality in color (dark red) of the lips, nailbeds, and mucous membranes occurs when the arterial blood oxygen saturation measures 75 to 85%. The oxygen tension at which this saturation of hemoglobin occurs is 32 to 42 mm Hg in the neonate because of the character of fetal hemoglobin and 42 to 54 mm Hg in the older infant after fetal hemoglobin has disappeared.

The amount of reduced hemoglobin in the circulating blood depends upon the total concentration of hemoglobin as well as the degree of desaturation of the arterial blood, i.e., the magnitude of the right-to-left shunt. The anemic infant with arterial blood oxygen desaturation therefore may not appear as cyanotic as the baby with polycythemia with the same percentage of desaturation. As was stated by Taussig in 1947, slight cyanosis in the infant with a hemoglobin level of 10 g may be a more ominous sign than deep cyanosis in the patient with a hemoglobin of 17 g.[8] Detection of cyanosis may be masked by skin pigment and may therefore be overlooked in black infants unless the tongue, mucous membranes, and nailbeds are examined. In the infant with a systemic blood oxygen arterial saturation of 85 to 90%, clinical cyanosis is usually not evident; however, desaturation may be suspected by virtue of a dark red discoloration of the fingers and toes.[9]

The importance of recognizing cyanosis is emphasized by the findings in the New England Regional Infant Cardiac Program, in which one third of infants with potentially lethal congenital heart disease had cyanosis as their major symptom and another third had cyanosis with respiratory symptoms.[10]

Differential cyanosis indicates cyanosis that is more pronounced either in the lower extremities than the upper or vice versa. In the first case, the usual pathologic cause is reversal of blood flow through a large ductus arteriosus so that the lower half of the body receives desaturated pulmonary arterial blood and the upper half receives the more highly saturated blood coming out of the left ventricle. There must be pulmonary hypertension at the systemic level for this to occur, and a difference of about 10 to 20 percentage points between the upper and lower extremities is required for the differential to be clinically apparent. Often, reversed flow through the ductus is not suspected on visual examination because the difference in oxygen saturation is too slight. If there is an associated large ventricular septal defect with considerable mixing at the ventricular level, the difference in oxygen saturation between the brachial and the femoral artery may be measurable only by oxygen analysis.

In transposition of the great arteries with pulmonary hypertension and large ductus, with the flow through the ductus from pulmonary artery to descending aorta, the upper half of the body has a lower saturation than the lower half, but again the difference has to be very pronounced to be seen clinically.

While differential cyanosis is an interesting phenomenon when observed, it occurs so rarely that it is seldom of much practical use from a diagnostic standpoint, and there are other, more reliable means of identifying the anomalies that produce differential cyanosis. Occasionally, despite equal oxygen saturation in upper and lower extremities, one gets the impression that the finger nailbeds are decidedly more cyanotic than the toe nailbeds. The explanation for this is not clear, but it is an important fact to keep in mind, since the clinician might erroneously suspect transposition of the great arteries with pulmonary hypertension and reversed flow through a ductus.

Other causes of cyanosis also may be arterial oxygen desaturation in association with respiratory diseases, hypoventilation related to central nervous system dysfunction, and abnormalities in the pattern of the transitional circulation of the newborn, e.g., persistent fetal circulation. Methemoglobinemia causes cyanosis, producing a lowered arterial blood oxygen saturation as measured by colorimeter methods but not by Van Slyke analysis or by oxygen tension (PO_2).[6] Methemoglobinemia is a rare cause of cyanosis but should be suspected if the arterial oxygen tension is normal and the oxygen saturation is low.[6]

Paroxysmal Hypoxemic Spells

Cyanotic attacks or hypoxemic spells need to be recognized and treated as an urgent matter. Although they are well described in many texts, it is important to know that these attacks are often misdiagnosed as "colic," seizures of nervous central origin, or sometimes the antics of an irritable and spoiled baby. Hypoxemic attacks can be very difficult for parents to recognize, and unless the physician actually witnesses a spell, it may be difficult to get

a clear history. A spell may simply be described as the behavior of a cyanotic infant that cannot be comforted.

The distinctive characteristic of spells is that the infant breathes quickly and with audible and visible distress. A close look at the infant's face will convince the examiner that the victim is in distress. While the arterial oxygen saturation does fall, so does the arterial blood pressure, and the resulting pallor may be more noticeable than increased cyanosis.

Spells may occur with those cardiac defects in which there is pulmonary stenosis or atresia in combination with an intracardiac communication. These are most common in tetralogy of Fallot but may occur in tricuspid atresia or even transposition. The attacks appear to occur in the infant who has only mild to moderate arterial desaturation at rest (a so-called "pink Tet"), and they are also more common and severe in the cyanotic child who is iron deficient.[8] They may occur in early infancy or first develop at 6 to 12 months of age. Taussig[8] noted a tendency to spontaneous improvement between 18 months and 2 years. Hypoxemic spells occur more frequently in the morning and after a feeding, although episodes can occur at any time of the day. They do not start during sleep. The probable sequence of events that leads to an attack consists of an initial decrease in systemic arterial resistance with a consequent increase in the magnitude of the right-to-left ventricular shunt. As a result, the arterial oxygen saturation drops to a critically low level. This presumably leads to a further decrease in systemic vascular resistance and progression of the hypoxemia. The development of metabolic acidosis compounds the problem. The respiratory center is stimulated by the decreased oxygen tension and decreased pH leading to hyperpnea. The infant becomes restless and agitated, thereby increasing the degree of cyanosis. Rarely, a clonic seizure may occur.

Associated with these symptoms, there is an increase in heart rate and a decrease or disappearance of the systolic murmur in tetralogy of Fallot as pulmonary blood flow decreases. This state usually resolves spontaneously after 1 to 5 minutes or may last for 20 to 30 minutes. These long-duration spells may end in death. Therefore recognizing spells early and providing for emergency surgical treatment are critical.

Squatting

Children with tetralogy of Fallot who are old enough to walk may squat down to rest after exertion. The infant who is not yet walking may pull up the legs in a bent-knee position when tired. Squatting is presumably a protective response to extreme hypoxemia in blood pressure in children with an intracardiac right-to-left shunt. There is great variability in the amount of exercise that a child with tetralogy of Fallot can tolerate before wanting to squat. In some instances, it is a matter of a few steps, while other children can undertake considerable activity before resorting to the squatting position. Squatting acutely increases systemic blood pressure, which reduces the right-to-left shunt and in effect improves pulmonary blood flow. Associated with the transient increase in blood pressure, the baroreceptors are stimulated, and via the vagus nerve, the heart rate slows.

Congestive Heart Failure

Heart failure occurs in some 30% of infants and children with congenital heart defects.[11] However, in those with serious cardiac lesions, 75% have congestive cardiac failure.[12] Of infants with congenital heart disease who develop cardiac failure, 90% do so during the first year of life.[13]

The earliest manifestation of congestive failure in infants may be a change in the pattern of respiration noted initially as simply tachypnea and, most extremely (and rarely), labored respiration with grunting and intercostal retraction.

Tachypnea

Tachypnea (Greek: "tachys" = swift; "pnoia" = breath) is defined as rapid, shallow respiration with a *persistently* fast rate of 60 beats or more per minute in the fasting, quiet newborn infant. Unlabored tachypnea may be overlooked unless the rate is counted for a full minute. Most healthy newborn infants under basal conditions have a respiratory rate of 45 to 60 breaths per minute; but after being fed, if restless, or after crying hard, the infant may have a respiratory rate that transiently increases to 80 to 100 per minute (Table 43–1).

In the infant with congestive cardiac failure, the increase in rate is a reflex response to an increase in pulmonary venous pressure or volume. This results from an increase in pulmonary blood flow because of a large left-to-right shunt or an anatomic obstruction to the return of pulmonary venous blood to the left heart. Alternatively, it may result from the increased hemodynamic resistance to left ventricular filling because of left ventricular failure and raised left ventricular end-diastolic pressure. This reflex is mediated at least in part by the vagus nerve and the J-receptors in the pulmonary interstitial space.[14,15] Talner[16] reported that modest elevation of pulmonary venous pressure to 8 to 10 mm Hg in the infant and 25 to 30 mm Hg in the adult may be associated with tachypnea. Increased capillary permeability and slower lymphatic drainage have been implicated as possible factors in this age difference.

Dyspnea

With increasing pulmonary congestion, the infant may become dyspneic (Greek: "dyspnoia" = difficult breathing) with grunting (i.e., forced expiration against a partially closed glottis), flaring of the alae nasi, and intercostal, suprasternal, and subcostal retraction. Compression of bronchi by dilated, tense, high-pressure pulmonary arteries may also contribute to increasing respiratory distress. The right middle lobe, left upper lobe, and left lower lobe bronchi are especially involved. There is also pressure on the bronchi by a distended left atrium within the angle of the carina.[17] This compression may lead to stasis of secretions within the tracheobronchial tree, causing areas of atelectasis and providing a nidus for infection. Air trapping may also occur secondary to edema of the bronchial or bronchiolar mucosa. This involvement of the respiratory tract causes coughing and wheezing and predisposes the infant to respiratory tract infections. In some infants, the respiratory problems dominate the clinical picture even in the absence of other signs of congestive cardiac failure and contribute to the failure to thrive, a result of the increased work of breathing.

Physical stresses for an infant include crying, large feedings, and defecation. Inquiry should be made into the breathing pattern and color following or associated with these activities. With congestive heart failure, an increased respiratory rate is common with feeding, grunting may be provoked, and panting is not unusual, especially if the infant has constipation.

Table 43–1. Respiratory Rate: Upper Limit

Birth–6 Weeks	*6 Weeks–2 Years*	*2–6 Years*	*6–10 Years*	*Over 10 Years*
45–60/min	40/min	30/min	25/min	20/min

Feeding Difficulty and Failure to Thrive

Feeding difficulty and failure to thrive are features that are commonly elicited from parents, although parents may not recognize their significance. The tachypneic and dyspneic infant lacks the energy to suck and tires quickly. The infant has to interrupt sucking in order to breathe and may fall asleep only to awaken again shortly afterward, irritable and apparently hungry. Alternatively, the infant may be lethargic and sleep excessively. Attempts to increase the volume of the feed may precipitate vomiting. Partly because of a deficient caloric intake, weight gain is poor. The extra work of breathing likewise contributes to growth failure. Much can be learned by listening carefully to the mother's or grandmother's observations, since a parent frequently has noticed rapid breathing or an alteration in the feeding pattern before it is observed by the attending medical staff. A normal infant can drink an age-appropriate amount (3 to 4 oz in the first month; 6 to 8 oz in older infants) in 20 minutes or less. Frequently, infants with heart failure require 30 or even 45 minutes to drink lesser quantities. In addition, parents may note a decrease in urine output, which could be caused by an inadequate intake of fluid or inadequate cardiac output.

Failure to thrive in infants with congenital heart disease has multiple contributing factors. In general, infants with large left-to-right shunts and/or chronic low cardiac output have the greatest problems, whereas infants with right heart obstructive lesions such as isolated pulmonary valve stenosis may grow normally or supernormally.[18] In some infants, growth remains poor despite an apparently normal caloric intake. Infants who have persistently fast and labored breathing may fail to gain weight because of the increased muscular work of continuous tachypnea. Under resting conditions, the oxygen cost of breathing is extremely small, less than 5% of the total resting oxygen consumption. With the increased respiratory effort associated with pulmonary congestion, the oxygen cost may increase to 30%.[19] Growth failure may have a genetic basis (e.g., short parents) in patients who also happen to have a congenital heart defect of a type unassociated with pulmonary congestion or low cardiac output.

Cheek and associates[20] have demonstrated that there is a reduction in the number of striated muscle cells in children with congenital heart disease, and Baum and Stern[21] have found a similar decrease in the number of adipose tissue cells in children with cyanotic congenital heart disease. It would therefore seem that chronic tissue hypoxia may interfere with cell replication. Since it appears that the adult complement of adipose cells is established by 1 year of age, chronic tissue hypoxia should theoretically be relieved early in life if an increase in adipose tissue cell and striated muscle cell number, leading to normal growth, is to be achieved.[22] Abnormalities of intestinal absorption add to the growth failure associated with a serious cardiac anomaly.[23] There is also some evidence to suggest that skeletal maturation may be retarded. White and associates[24] noted a deficiency of cortical bone growth in children and adolescents with congenital heart disease.

Sweating and Pallor

Traditionally, we are taught that excessive sweating in the infant with congestive cardiac failure results from increased sympathetic nervous system activity, as do pallor and tachycardia. However, the increased work of breathing also contributes in a great measure to sweating. Pallor results from constriction of the skin arterioles, the body's compensatory mechanism for a reduced cardiac output, to divert the available blood pool away from nonessential areas. Physicians often mistake the pallor for evidence of anemia.

Exercise Tolerance

Many patients exhibit no noticeable symptoms despite a structurally important congenital heart defect. For example, children with pulmonary stenosis, aortic stenosis, coarctation of the aorta, or atrial septal defect frequently participate in all normal activities. Their parents deny that the child has any noticeable exercise limitation. However, inadequate cardiac output, raised pulmonary venous pressure, or severely reduced pulmonary blood flow produces fatigue, shortness of breath, syncope, or a faint feeling if the circulation is stressed. The sensation of fatigue stems directly from ischemia of exercised muscle and, in patients with inadequate cardiac output, is ascribed to oxygen debt and local deficiency in blood flow.[25] Exercise intolerance can be a difficult symptom to gauge accurately in children, since children show a great variation in degree of interest and coordination ability for physical activity. Frequently, children are not aware of exercise intolerance until their defect is repaired, and they know "normal" for the first time. Customarily, we grade exercise intolerance using the New York Heart Association grading system I to IV. This classification is useful in taking a history from adolescents who are articulate. But in younger children, the accuracy of this subjective grading system is low. The physician must depend upon the reliability of games the observers have watched the child play or exercise in comparison with presumed healthy playmates. A structured exercise stress test may be needed to accurately evaluate exercise tolerance.

In pulmonary valve stenosis, easy fatigability and dyspnea occur with only very severe obstruction, enough to initially reduce the volume of blood flow returning to the left heart. In aortic stenosis, easy fatigability, angina, or syncope occurs with very severe stenosis.[26] However, we often encounter the patient with a high grade of obstruction who denies exercise-induced fatigue, angina, or syncope. As long as the hypertrophic left ventricle can eject an adequate stroke volume, although at the expense of high left ventricular pressure, the patient may remain free of symptoms. Objective signs of myocardial ischemia may be uncovered by exercise stress tests in the asymptomatic patient.

Sudden Death

Sudden "unexpected" death may occur in association with cardiovascular disease in children. In a large cooperative international study, over half of the patients who died suddenly were inactive at the time; only 10% were engaged in active sports. A previous history of syncope occurred in only 16%. Among children who had had no previous cardiac surgery, aortic stenosis was the most

common lesion. Both obstructive and nonobstructive cardiomyopathies were present in 16%, while 25% of the patients who had had no previous surgery had either Eisenmenger's syndrome or cyanotic congenital heart disease with pulmonary stenosis.[27] A history of either dizziness or syncope, especially that which is exercise induced, should be regarded seriously and investigated further. Glew and associates have stated that death in patients with aortic stenosis is often sudden but hardly "unexpected" if one considers not only a history but also the physical examination and the resting and exercise electrocardiogram.[28] A more complete discussion of sudden death may be found in Chapter 108.

Arrhythmias

In addition to the structural cardiac defects mentioned, arrhythmias may predispose the patient to sudden death. The lethal primary arrhythmias include prolonged Q-T interval syndrome, catecholamine-sensitive ventricular tachycardias, atrial fibrillation associated with the Wolff-Parkinson-White syndrome, and congenital complete AV block. A history of resting- or exercise-induced dizziness or syncope in patients with one of these arrhythmias should be considered a warning sign.

A child 5 years of age or older may be able to answer questions about precipitating events of syncope. Was the patient exercising or frightened before the dizziness or fainting occurred? Was there chest discomfort or palpitations? Was there any particular pattern to the occurrence of the episodes? For example, a girl first developed syncope at 8 years of age at a road junction on her way to school. She was diagnosed as having epilepsy. By 11 years of age, the episodes occurred almost exclusively at this spot. She became convinced that they were going to recur and would become alarmed and frightened when approaching the junction. Ventricular tachycardia was documented in association with the Romano-Ward syndrome of prolonged Q-T interval on the electrocardiogram. A 10-year-old child wih a normal Q-T interval had recurrent episodes of polymorphic ventricular tachycardia with exercise, and multiple episodes were also precipitated while in the hospital, during blood tests.

Benign vasovagal episodes are usually unassociated with exercise but may be brought on by emotional stress or by standing for long periods of time, especially if food or fluid intake has been inadequate. A resting, an exercise, and often a 24-hour ambulatory electrocardiogram may be helpful to determine whether the syncope is associated with an arrhythmia and by taking the blood pressure supine and after standing for 10 minutes.

Chest Pain

Chest pain is a fairly common complaint in individuals who prove to be healthy and in whom no pathologic cause can be identified. Inquiry should be made about family history of angina, recent cardiac deaths, school or family stress, separation, and the like. In the vast majority of cases, the chest pain has no organic basis. Chest pain may be a conversion symptom, but it may also be a symptom associated with depression even in children.[29] It is important, however, to identify those patients in whom chest pain has a cardiac cause. Such patients can be divided into three categories: patients with structural abnormalities, e.g., left ventricular outflow tract obstructive lesions, mitral valve prolapse, or congenital coronary anomalies; patients with acquired myopericardial disease, e.g., pericarditis, coronary disease, or previous history of Kawasaki disease; and patients with arrhythmias. Organic cardiac pain is usually a pressure or squeezing sensation rather than a sharp pain. It tends to be central in location rather than apical or lateral on the chest. It is not usually affected by respiration. It may be brought on by exertion and relieved by rest, and it carries greater significance if it is associated with dyspnea or syncope and/or palpitations.

The relationship of the pain to respiration should be questioned, since pain may occur with hyperventilation. The common benign "stitch" or precordial catch is usually aggravated by a deep breath.

Any relationship of pain to meals should be documented. An esophageal or gastrointestinal cause is found in about 20% of adults presenting with chest pain, but this is a rare cause in children.[30]

Chest pain in an otherwise well child is usually benign, especially if the pain is sharp in nature, laterally located on the chest, and brief in duration. The exact cause of chest pain remains uncertain in 40 to 50% of patients even after investigation.[31] Despite this, a careful history and physical examination are a sensitive means of discriminating between organic cardiac chest pain and nonorganic causes of chest pain.[30] As with the evaluation of murmurs, it is essential that anxiety is not unwittingly created in the child or family by an inconclusive evaluation. Physicians have the responsibility to identify pathology if it is present but also to avoid creating anxiety when no disease exists.

Past Medical History

History of previous important illnesses, medications, and hospitalizations may prove to be relevant. Was there any history to suggest myocarditis in the past in an infant or child who now presents with a congestive cardiomyopathy or endocardial fibroelastosis, or was there any history of exposure to potentially cardiotoxic drugs? For example, if doxorubicin hydrochloride (Adriamycin) is administered in a dose greater than 600 mg/m^3, a congestive cardiomyopathy occurs in more than 30% of cases.[32] Disopyramide, quinidine, and propranolol are negatively inotropic and may precipitate congestive cardiac failure.[33]

In a review of children with Hodgkin's disease, Greenwood and associates found that 7% of those who received thoracic irradiation developed constrictive pericarditis.[34]

Immunizations

The immunization record should be checked, since a significant number of infants either do not receive immunization at all or are immunized well after the recommended dates. Except for the critically ill infant with heart disease, immunizations should not be delayed, since pertussis and rubeola are especially dangerous for such patients.

Development and the Central Nervous System

Inquiries should be made regarding motor and intellectual development. While the majority of children with congenital heart disease display normal development, a few have coexisting intellectual, perceptual, or motor handicaps.[18] It is especially pertinent to know whether such problems exist before an operation to avoid the suspicion that the surgery may have led to the disability. Whenever possible, details should be documented preoperatively. Neurologic complications may occur in association with cyanotic heart disease; in particular, a history of stroke should be carefully elicited. Stroke is more common in children under two years of

age. It is more likely to occur in association with iron deficiency and with a systemic arterial oxygen saturation of 50% or less.

Headaches in patients with polycythemia may result from the intravascular plethora or could be the result of bone pain in older children and adolescents with marked polycythemia. Persistent severe headaches in the child who has coarctation of the aorta are a possible, but rare, manifestation of cerebral arterial aneurysm.

Pyrexia

A presenting complaint or prior history of an inflammatory illness in the patient with cardiac findings prompts investigation for Kawasaki disease, rheumatic fever, myocarditis, or endocarditis. In the infant under 2 years of age, Kawasaki disease is the most likely. Physicians in the 1980s are familiar with the manifestations of what appears to be a newly recognized disease (Chapter 89). Similarly for rheumatic fever, the major and minor Jones criteria should be sought by careful inquiry (Chapter 86).

A history of headache, vomiting, and undue somnolence with fever in the cyanotic child should lead one to suspect brain abscess.

While an identifiable cause for a bacteremia preceding endocarditis is obtainable in only about one third of cases, it is important to ask about the state of dental health, dental therapy, or other procedure that might have led to a bacteremia. Unrecognized dental abscess is an important cause. If a procedure was performed, it is important to determine whether antibiotic prophylaxis was given, its form, and the time sequence of administration.

History of the Pregnancy, Especially the First Three Months

It is important to take a detailed history to ascertain drug exposure or viral infection during the first 3 months of pregnancy, even though only 2% of congenital heart disease is considered to have an environmental etiology.[35] Table 43–2 lists some of the known teratogens.[36–45] In many cases, exposure to one of these agents has devastating effects on the developing fetus. Rubella causes not only cardiac anomalies (pulmonary branch stenosis and patent ductus arteriosus) but also blindness, deafness, and microcephaly with associated profound developmental delay.[36] It is tragic to see infants with the maternal rubella syndrome when it is so readily preventable. Similarly, the fetal alcohol syndrome and some of the other drug-related disturbances in morphogenesis can be prevented.[37] In some instances, the observation of drug exposure may require a modification of therapy during pregnancy rather than withdrawal of treatment as, for example, in the epileptic mother.[38,39] While there is strong evidence to implicate the causative factors outlined in Table 43–2, there is also some evidence to suggest that the amphetamines and sex hormones and perhaps infection with cytomegalovirus and coxsackievirus in early pregnancy may cause cardiac anomalies.[45]

Table 43–2. Teratogens

Causative Factor	*Risk of CHD*	*Defect*
Infection		
Rubella (1941)	50–80%	PDA, PBS, VSD
Drugs		
Diphenylhydantoin		
Fetal hydantoin syndrome (1975)	10%	PS, AS
Trimethadione		
Fetal trimethadione syndrome (1975)	50%	VSD, TF
Thalidomide (1962)	20%	TF, TA
Lithium (1974)	10%	Ebstein's anomaly
Alcohol		
Fetal alcohol syndrome (1973)	30–40%	VSD, ASD
Maternal Diseases		
Diabetes	3–4%	VSD, TGA, cardiomyopathy
Lupus erythematosus	?	complete AV block

Date (■) = when association first published.
PDA = patent ductus arteriosus.
PBS = pulmonary branch stenosis.
VSD = ventricular septal defect.
TGA = transposition of the great arteries.
PS = pulmonary stenosis.
AS = aortic stenosis.
TF = tetralogy of Fallot.
TA = truncus arteriosus.
ASD = atrial septal defect.

The Mother's Health

If the mother has diabetes, the fetus has a risk of congenital heart disease that is three to four times greater than that in the general population.[44] Ventricular septal defect and transposition of the great arteries are particularly common. In addition, there is a specific cardiomyopathy in the infant of the diabetic mother that is closely analogous to the hypertrophic cardiomyopathy of older children and adults but that regresses spontaneously in the majority.

In 1966, Hull and associates noted an interesting association between congenital complete AV block in the fetus and the presence of lupus erythematosus in the mother.[46] Since then, many studies have indicated that congenital AV block in the infant may precede the overt clinical manifestations of systemic lupus erythematosus in the mother by months or even years.[47]

In the latter part of pregnancy, particularly in the week or so prior to delivery, a coxsackievirus infection in the mother may cause acute myocarditis in the newborn infant. This can be a fulminant disorder associated with a high mortality. The illness in the mother may be a simple respiratory infection with or without pleurodynia.[48] The rubella virus may also cause myocardial cell injury and necrosis.[49]

Family History

Details of the family history should be explored because of the potential genetic implications. Inquiries should be made as to whether either parent has or had a congenital heart defect, and details of all siblings should also be clearly documented. The number of stillbirths and spontaneous abortions should be recorded, though it appears from studies by Warburton and Fraser that the incidence of these events in mothers who have children with congenital heart disease is the same as that in the general population, i.e., 1 to 1.5% stillbirths and 14 to 15% spontaneous abortions.[50]

If one parent is affected or if a previous sibling had a congenital heart defect, the risk of a recurrence is 1 to 5% depending on the type of defect previously documented. Recurrence is higher with

the more common defects; the risk is on the order of 4 to 5% if a first-degree relative has a ventricular septal defect. If there are two affected first-degree relatives, the risk is tripled. In the unlikely event of three affected first-degree relatives, a family would have to be considered a type C family in Nora's classification and therefore have a high recurrence risk on the order of 60 to 100%, i.e., significantly greater than that of a mendelian dominant lesion.[35]

In the New England Regional Cardiac Program, approximately one third of patients with congenital heart disease were found to have a positive family history of a congenital cardiac anomaly. There was also a concordance of defect in approximately 50% of cases.[10,51]

With increased survival following the successful management of infants and children with congenital heart disease, more people with congenital heart disease are reaching child-bearing age and therefore potentially increasing the risk of structural heart defects in their offspring. Recent data imply approximately a 10 to 15% risk of congenital heart disease in the offspring of mothers with congenital heart disease.

Careful inquiry should also be made about syndromes in the parents or in their immediate relatives that have dominant inheritance, e.g., Marfan and Holt-Oram syndromes or a recessive inheritance trait such as Friedreich's ataxia, cutis laxa, or pseudoxanthoma elasticum. About 8% of congenital heart defects have a genetic or chromosomal basis.[35]

One of the benefits of taking a history from the parents is that it gives the physician an opportunity to assess the family structure and the interaction between the parents, as well as between the parents and child. It also allows an initial assessment of the parents' capacity to comprehend an explanation of a cardiac lesion and of their ability to cope if their infant or child is going to require intensive investigations and perhaps surgical treatment.

Birth History

Details about the progress of labor, the method of delivery, and the Apgar score should be recorded. The importance of ascertaining these facts relates primarily to the differential diagnosis of infants with congenital heart disease. Asphyxia during labor or in association with delivery may be associated with persistence of the fetal circulation. This may manifest clinically as a very cyanotic infant with persistent pulmonary hypertension, transient myocardial ischemia, myocardial dysfunction, and congestive cardiac failure or simply as transient tachypnea.[52] The distinction from structural cardiac defects may require detailed investigations such as echocardiography or, rarely, cardiac catheterization. In addition, the stressed newborn infant may suffer from hypoglycemia and hypocalcemia, which may be associated with heart failure. Delay in clamping the umbilical cord or fetal-to-fetal transfusion in the case of twins may give rise to significant polycythemia, volume overload, and congestive cardiac failure.

Birth Weight

In the New England Regional Infant Cardiac Program, the birth weight of 2178 infants with 21 different cardiac diagnoses demonstrated that in all diagnostic categories except for d-transposition, pulmonary stenosis, and hypoplastic left heart, there was an abnormally low birth weight distribution.[53] This distribution was not affected significantly by major extracardiac anomalies. However, Noonan and Ehmke have noted that among infants with multiple extracardiac anomalies and congenital heart disease, over 60% are in the low-birth-weight group.[54] It is also clear from studies of Fyler and associates that infants of low birth weight have a poorer survival rate than do infants of normal birth weight and comparable heart defects.[51]

The premature infant has an increased incidence of ventricular septal defect and, of course, patent ductus arteriosus,[55] the latter usually in association with pulmonary disease.

At the other end of the spectrum, the baby that is large for gestational age, e.g., the infant of the diabetic mother, has three to four times the risk of congenital heart disease than does the general population. The infant with Beckwith-Wiedemann syndrome has a 50% incidence of congenital heart disease.[56,57]

Sex

Coarctation of the aorta, aortic valve stenosis and transposition of the great arteries are more common in male infants than in female infants. In female infants, two anomalies are more common than in males: septal defect and patent ductus arteriosus.

Review of Other Systems

A review of the other systems is a very important part of the clinical assessment, since extracardiac malformations are common and have been detected in about 25% of patients with congenital heart disease in clinical series and up to 45% in autopsy series.[58,59]

Abnormalities of the skeletal, gastrointestinal, genitourinary, and central nervous systems have all been described. According to Greenwood and associates, a "syndrome" of some type is present in 8.5% of infants with congenital heart disease.[58] It is therefore important that specific syndromes are recognized so that proper genetic counseling and patient management can be undertaken. Table 43–3 lists some cardiac defects that are found in association with the more common syndromes.[60] The commonest is Down syndrome, which occurs in 4% of infants with congenital heart disease. Of the children with Down syndrome, 40% have

Table 43–3. Common Syndromes and Associated Cardiac Defects

Syndrome	*Defect*
Down syndrome (1866) (trisomy 21)	atrioventricular septal defect
Edwards' syndrome (1960) (trisomy 18)	double outlet right ventricle ventricular septal defect
Patau's syndrome (1960) (trisomy 13)	ventricular septal defect
Turner's syndrome (1938) (XO)	coarctation, aortic valve stenosis
Noonan's syndrome (1968)	pulmonary stenosis hypertrophic cardiomyopathy
Williams syndrome (1961) (idiopathic hypercalcemic syndrome)	supravalvular aortic stenosis
Asymmetrical cry (1967)	ventricular septal defect tetralogy of Fallot
Carpenter's syndrome (1901)	patent ductus arteriosus ventricular septal defect

congenital heart disease, and approximately 40% of those have an endocardial cushion defect.[61]

Skeletal Abnormalities

Skeletal abnormalities represented 32.5% of the anomalies reported by Lamy and associates in association with congenital heart disease excluding Down syndrome.[62]

Vertebral anomalies are uncommon in isolated congenital heart disease and are usually present as part of a more complex syndrome, e.g., the VATER or VACTERL syndrome.[54,63] Nora and associates have noted that in the Klippel-Feil syndrome, congenital heart disease becomes more frequent with increasing degrees of cervical vertebral fusion.[64]

Scoliosis

Scoliosis is an important association and has been described in 2% of children with acyanotic congenital heart disease and 6% of those with cyanotic disorders. In most instances, scoliosis appears to be of the idiopathic variety; but in 15% of cases, there are associated vertebral anomalies.[65]

The Straight Back Syndrome

The straight back syndrome, which is caused by loss of the normal physiologic dorsal thoracic kyphosis, may have findings on cardiac examination that are suggestive of mild pulmonary valve stenosis or an atrial septal defect in the presence of a structurally normal heart. A murmur that is indicative of mild pulmonary regurgitation may be present in some cases. The anterior cardiac displacement in this entity appears to be the result of a more anterior insertion or attachment of the pericardium to the diaphragm rather than simply due to the narrow anteroposterior diameter of the chest.[66]

Identification of certain abnormalities of the hand and forearm may aid in the recognition of syndromes and therefore alert the physician to the possibility of a specific type of cardiac abnormality.[67,68] Table 43–4 outlines some of these diagnostic features and indicates the more common cardiac defects found with specific syndromes.

Palmar Creases

Single palmar creases, while present unilaterally in 4% and bilaterally in 1% of the normal Caucasian population, are frequently found in children with Down, trisomy 13, cri du chat, and de Lange's syndromes.[60]

Polydactyly

Polydactyly is present in the syndromes outlined in Table 43–4, and associated cardiac defects are found in 80% of infants with trisomy 13 syndrome and in more than 50% of those with Ellis-van Creveld syndrome. Cardiac lesions are less commonly diagnosed in Carpenter's syndrome and rarely with the Laurence-Moon-Beidl syndrome. Excluding trisomy 13 syndrome, the other three disorders are recessively inherited.[60]

Thumb Abnormalities with or without Anomalies of the Radius

Abnormalities of the thumb and radius can vary from hypoplasia to aplasia. In the Holt-Oram syndrome, the thumb may be absent or resemble a finger and be triphalangeal.[69] The Holt-Oram syndrome is a dominantly inherited disorder, while Fanconi's syndrome and radial aplasia with thrombocythemia are recessively inherited.[70,71]

Unilateral absence of the thumb or radius may also be part of a multiple anomaly syndrome such as the VATER syndrome.[63] In addition, Noonan has noted that hypoplasia of the thumb or radius when not part of a multiple anomaly syndrome is usually associated with a ventricular septal defect and severe pulmonary hypertension.[61] The term ventriculoradial dysplasia has been used to describe this association.[72] Gross abnormality of the upper limb, e.g., phocomelia, was seen following maternal exposure to tha-

Table 43–4. Abnormalities of the Hand and Forearm in the Detection of Disorders with Associated Congenital Heart Disease

Single Palmar Crease	
Down syndrome[67] (1866)	AV canal, VSD, PDA, TF
Patau's syndrome[67] (1960)	VSD, PDA
Cri du chat syndrome[67] (1963)	VSD, TA
De Lange's syndrome[67] (1933)	VSD
Polydactyly	
Ellis-van Creveld syndrome[67] (1940)	single atrium
Patau's syndrome[67] (1960)	VSD, PDA
Laurence-Moon-Biedl syndrome[67] (1865)	PDA, TGA, PS
Carpenter's syndrome[67] (1901)	VSD, ASD
Thumb Abnormalities and Abnormality of Radius	
Holt-Oram syndrome[69] (1960)	ASD
Fanconi's syndrome[70] (1967)	PDA
Thrombocytopenia-absent radius syndrome[71] (1969)	TF
Ventriculoradial dysplasia[72] (1966)	VSD
VATER syndrome[63] (1972)	VSD
Rubinstein-Taybi syndrome[67] (1963)	PDA
Phocomelia	
Thalidomide[40] (1962)	TF, VSD
De Lange's syndrome[67] (1933)	VSD
Arachnodactyly	
Marfan syndrome[67] (1896)	MVP, MR, AI, aneurysm
Homocystinuria[67] (1963)	thrombosis of medium-sized arteries
Hypoplastic Dysplastic Nail	
Turner's syndrome[67] (1938)	coarctation, AS
Fetal hydantoin syndrome[38] (1975)	PS
Ellis-van Creveld syndrome	single atrium
Trisomy 13 syndrome (Patau)	VSD
Trisomy 18 syndrome (Edwards')	DORV, VSD

Date (■) = when syndrome first described.
AV Canal = atrioventricular canal.
VSD = ventricular septal defect.
PDA = patent ductus arteriosus.
TF = tetralogy of Fallot.
TA = truncus arteriosus.
ASD = atrial septal defect.
MVP = mitral valve prolapse.
MR = mitral regurgitation.
AI = aortic insufficiency.
AS = aortic stenosis.
PS = pulmonary stenosis.
DORV = double-outlet right ventricle.
TGA = transposition of the great arteries.

lidomide, but these defects may also occur in association with de Lange's syndrome.[40,41,60] Broad thumbs are characteristically present in Rubinstein-Taybi syndrome.[60] Cardiac defects are only occasionally seen in association with Rubinstein-Taybi syndrome.[60]

Arachnodactyly

Arachnodactyly is a characteristic finding in Marfan syndrome, a dominantly inherited disorder, in which mitral valve prolapse, mitral regurgitation, aortic aneurysm, and aortic insufficiency are common and progressive abnormalities.[60]

Other abnormalities of the hands that may give diagnostic information include hypoplastic or dysplastic nails seen in association with Ellis-van Creveld syndrome, Turner's syndrome, and both trisomy 13 and trisomy 18. In trisomy 18, there is also a characteristic clenched fist with overlapping fingers, the index finger over the third and the fifth over the fourth. Lymphedema may be present in neonatal Turner's syndrome. Congenital heart disease is present in approximately 25% of infants with Turner's syndrome, and 70% of these have coarctation of the aorta.[60]

Gastrointestinal Tract

In studies on infants with various gastrointestinal abnormalities such as tracheoesophageal fistula, omphalocele, imperforate anus, and diaphragmatic hernia, Greenwood and associates have documented an incidence of congenital heart disease that varies between 12 and 23%.[73–76] The prognosis is significantly altered by the presence of the congenital heart defect, which is therefore important to recognize for the proper management of infants with these abnormalities. Boesen and associates noted that there was an increased incidence of tetralogy of Fallot in children with gastrointestinal anomalies, whereas ventricular septal defects were more common in association with bone and joint abnormalities.[77]

Genitourinary Anomalies

Mehrizi reported a 4 to 15% incidence of renal anomalies in autopsy studies on patients with congenital heart disease.[78] The renal anomalies are often clinically silent; and unless the coexistence with congenital heart disease is remembered, significant abnormalities may be overlooked.

PHYSICAL EXAMINATION

In general, the traditional examination format of inspection, palpation, percussion, and auscultation should be followed, but the subject must be reasonably quiet for each step. The small infant up to nine months of age is generally easily distracted and enjoys eye and social contact. The infant at this age may also be quieted with a pacifier or can be fed during part of the examination. Infants from nine months to two years of age may be apprehensive. The examiner should allow a few minutes for the infant to become accustomed to the physician's presence before beginning the examination. Have toys available that can be used to distract the infant. Sometimes allowing the patient to hold the head of the stethoscope gives reassurance. Examination of the toddler is often best performed with the child on the parent's lap; complete evaluation in both the supine and erect postures can be carried out without difficulty. The child from three years of age upward usually cooperates for the cardiac examination.

The weight and height are measured and compared to the range of normal on a growth chart. In infants, it is usually preferable to leave these measurements and the measurement of the blood pressure until the end of the examination, since they may upset the infant. The most important initial step is to assess whether the infant or child is acutely or potentially stressed and therefore in need of urgent investigation and management. Second, is the infant cyanotic or acyanotic? Third, is the infant or child outwardly well within minimal symptoms or asymptomatic?

The infant with initial cardiac disease has either resting or stress-induced hypoxemia, pulmonary edema, right heart failure, reduced right or left ventricular output, or a combination of these pathophysiologic states. The sick infant often appears anxious; may have pallor, sweating, tachypnea, and dyspnea; and dislikes being handled. The hypoxemic infant also tolerates handling poorly. In both instances, the examination should be carried out gently and with as little disturbance to the infant as possible. Much useful information about cardiorespiratory function can be obtained from inspection of the infant alone. If the infant is asleep as the examiner enters the room, take the opportunity to measure the respiratory rate. This should be recorded for at least 30 seconds and preferably a full minute.

Is there skin pallor to suggest low cardiac output? Is the infant cyanotic or acyanotic? Is there evidence of clubbing? Any dysmorphic features should be noted carefully.

The analysis of the clinical evaluation should be critical, and definitive diagnostic conclusions should not be made about the crying or upset infant or child. This applies to the assessment of pulses, blood pressure, heart sounds, and murmurs.

Clubbing

Clubbing was recognized by Hippocrates[79] as a sign of empyema. Today, pediatricians first think of clubbing as a manifestation of cyanotic congenital heart disease. Clubbing due to cyanotic heart disease is not present at birth and is rare before three months of age. It is caused by thickening of the tissues at the base of the nail, which is secondary to capillary engorgement in association with chronic hypoxemia and polycythemia. As a result of this, the angle between the base of the nail and the adjacent skin of the finger or toe is obliterated. The skin becomes shiny, and there is increased compressibility of the nailbed. With progression, the nail loses its longitudinal ridges and becomes convex. In extreme cases, the terminal segment of the finger and/or toe is bulbous, like the end of a drumstick.

While clubbing is usually easy to recognize, there are times when the changes are mild. The measurement of the depth (from nail to palmar surface) of the index finger at the base of the nail divided by the depth at the distal interphalangeal joint may clarify the issue. A ratio that is greater than 1 is abnormal and indicates clubbing. This relationship is independent of age, sex, and race.[80]

Mild clubbing may be present when the systemic arterial blood oxygen saturation is 85 to 90%, a level at which cyanosis may not be clinically apparent. In this circumstance, the fingers and toes may have a dark red appearance.

Taussig observed that clubbing may regress in the presence of anemia.[8] It also resolves when the chronic hypoxemic stimulus has been removed by corrective cardiac surgery. Cyanosis without clubbing after the age of two years indicates that the cyanosis has been of short duration and may indicate reversal of a shunt caused by increasing pulmonary vascular resistance.[8]

Pulses

Pulses are assessed for rate, rhythm, volume, and character. The pulse character is an approximate indicator of the cardiac output unless isolated anomalies of the aortic arch vessels or the aorta damp the arterial pulse.

The criterion for tachycardia during physical examination is a heart rate of 150 beats or more per minute in the resting infant and 120 beats or more per minute in the child (Table 43–5). A phasic variation in the heart rate during respiration (faster with inspiration) indicates physiologic sinus arrhythmia. It is usually not obvious in healthy infants, since at a fast heart rate, sinus arrhythmia is not ordinarily detected clinically. A pulse deficit (i.e., a difference in the heart rate counted with the peripheral pulse compared to that determined by auscultation at the cardiac apex) is commonly appreciated in the presence of ectopic beats.

A sinus tachycardia may be an attempt on the part of the infant to increase cardiac output in the presence of increased tissue needs for oxygen or an inadequate delivery of oxygen for whatever reason.[81] Pallor and sweating are frequently evident in association with tachycardia. A heart rate of greater than 220 beats per minute would suggest paroxysmal supraventricular tachycardia.

Pulse Volume

It may be helpful when assessing the volume of the pulse and especially when comparing the brachial and femoral pulses to compress the pulse to the point of obliteration and then slowly release the pressure while assessing the comparative volume of each pulse. A difference in volume may be more readily detectable and also more sensitive in the diagnosis of coarctation of the aorta than trying to appreciate a delay in the peak of the pulse in a small infant with a heart rate of 150 to 180 beats per minute. To assess the pulses accurately, the infant must be relaxed and quiet. Many times in the tense infant, a femoral pulse will seem to be absent only to appear to be of normal volume when the infant relaxes. It is also of value to feel the pedal pulses if the femorals are difficult to palpate or as an initial step when an infant is sitting on the parent's lap before being placed supine. It should be remembered that the dorsalis pedis pulse is congenitally absent in about 10% of the population.[82]

An increase in pulse volume is most commonly associated with pyrexia, with anemia, following exercise, and with thyrotoxicosis. A marked increase in the pulse volume with a pulse pressure greater than 30 mm Hg in the infant and 50 mm Hg in the child gives rise to a bounding pulse. The presence of a bounding pulse in an infant or young child is most commonly caused by a moderate or large ductus arteriosus. It may also occur in the presence of aortic insufficiency or with truncus arteriosus when there is either a rapid runoff into the lungs or truncal valve insufficiency. An increased pulse volume is found with an arteriovenous fistula irrespective of site.

A diminution in pulse volume occurs in the presence of low cardiac output from any cause. The frequent structural causes of diffuse diminution in pulse volume are left heart obstructive lesions and particularly aortic valve atresia or stenosis. In the early phase of congestive cardiac failure due to hypoplastic left heart syndrome, aortic valve atresia or critical stenosis may be clinically suspected when the right arm pulse has a lower volume than the left arm or femoral pulse. As the ductus closes and the clinical condition deteriorates, all pulses become nonpalpable. Children with aortic stenosis may have a pulse of normal volume and character; but with careful attention to the upstroke of the pulse, a delay or slurring may be appreciated even when the volume of the pulse appears to be normal.

Table 43–5. Normal Average Pulse Rate at Different Ages

1 week	*1 year*	*6 years*	*Puberty*
140/min	120/min	100/min	80/min

In supravalvular aortic stenosis, there may be a discrepancy in the pulse volume between the right and left arms. The right arm pulse is stronger because of the Coanda effect, i.e., a tendency for a fluid jet to adhere to a wall.[83] In supravalvular aortic stenosis, there is an increased proportion of the ejected volume from the left ventricle deviated toward the innominate artery and therefore the right arm.

The right arm pulse is also stronger than the left in the presence of coarctation when the left subclavian artery is involved in the coarctation. On rare occasions, the left subclavian artery may be involved in the coarctation, and the right subclavian artery may arise from the descending aorta distal to the coarctation and travel in a retroesophageal manner to the right arm, giving rise to four-limb diminution in pulses. The carotid pulses in this circumstance have increased volume. An increased carotid pulsation is also evident with patent ductus arteriosus, with aortic insufficiency, and in the rare anomaly cerebral arteriovenous malformation. Unilateral prominent neck pulsation can be found in the presence of a cervical aortic arch, and transient compression of this pulsation causes obliteration of the femoral pulse.[84]

Prompt distension and a quick, visible collapse of the carotid arteries were described by Dominic Corrigan in 1832. In addition, the palpable findings of the arterial pulse were described in Corrigan's classic paper on physical findings in aortic regurgitation. The finding of a sudden palpable shock when the artery rapidly fills was likened to the water hammer, a Victorian toy with a small amount of fluid in a vacuum tube, by Watson in 1843. The alternation of flushing and pallor of the skin with systole and diastole (the capillary pulse) was described by Quincke in 1868. This capillary pulse may be seen with partial compression of the tip of the fingernail or with a glass slide pressed against the earlobe. Corrigan's pulses, water hammer pulses, and Quincke's pulses are all characteristic of severe aortic regurgitation but may be found in other settings with a marked diastolic runoff (such as a case of truncus arteriosus or a large ductus arteriosus with low pulmonary vascular resistance).

Pulsus Paradoxus

Pulsus paradoxus, which is an exaggeration of the normal inspiratory and expiratory variation in blood pressure, may be found in association with constrictive pericarditis, cardiac tamponade, cardiac failure, or severe respiratory distress, such as asthma. This variation may be appreciated on palpation of the pulse but is more accurately assessed while taking the blood pressure. If there is a difference of 10 mm Hg or greater between the recorded systolic pressure during expiration and that recorded during inspiration, then a significant degree of paradox is present.[85] Pulsus paradoxus was considered "paradoxical" because in the setting of tamponade, the venous pressure was noted to rise (Kussmaul's sign)

during inspiration while the arterial pressure dropped during inspiration.

Pulsus Alternans

Pulsus alternans (Traube's sign), an alternating strong and weak pulse, is a rare and late but reliable sign of severe left ventricular failure and can be appreciated on palpation of the pulse and also while recording the blood pressure.[85]

Pulsus Bisferiens

Pulsus bisferiens is a pulse with a double peak, i.e., a prominent percussion and tidal wave separated by a midsystolic cleft, which may be found in lesions with a large left ventricular stroke output such as a patent ductus arteriosus or aortic regurgitation.[85] In hypertrophic cardiomyopathy with obstruction, the pulse characteristically has a very rapid upstroke; this is followed by an extended plateau. This pulse abnormality may be minimal or absent at rest but can be exaggerated by Valsalva's maneuver or by inhalation of amyl nitrite.[85]

Blood Pressure

After assessment of the pulse contour, the next logical step is to take the blood pressure. However, as was stated earlier, it is best to leave this part of the examination until the end in children under three years of age, since the sensation of pressure on the arm is uncomfortable and may provoke crying. The recording of blood pressure in children should be part of every cardiovascular examination and is not difficult in a child. Obtaining an accurate blood pressure in infants is one of the most technically difficult parts of the examination to perform. There is no point in recording blood pressures obtained in the crying or restless infant or child. Maximum distraction is required during this evaluation to try to prevent the infant from becoming restless or agitated. In children and adults, the systolic pressure in the lower limb is some 10 mm Hg (or even up to 20 mm Hg) higher than in the upper limbs using the same-sized blood pressure cuff. In infants, the systolic pressures are the same, but at no age should the pressure in the lower limb be less than that in the upper limbs. A higher pressure in the upper limbs with a pressure difference of 10 mm Hg or greater between the upper and the lower limbs indicates coarctation of the aorta.

The methods available for obtaining blood pressure are discussed in detail in Chapter 30 and are summarized in Table 43–6. To record an accurate blood pressure, use a cuff size in which the inflatable rubber bag covers two thirds of the upper arm or the width of the bag rather than the cloth cover, which is equal to half the circumference of the upper arm. This means in practice using a cuff that covers the upper arm just leaving the antecubital fossa available for auscultation or palpation. When applied, the inflatable bag should completely encircle the arm so that uniform compression may be obtained. Too short a bag may lead to erroneously elevated blood pressure readings from the mercury manometer. A similar problem may arise if the width of the cuff is too narrow; this is one of the commonest causes of apparent hypertension. If an ideal cuff is not available, then use one that is a little too big rather than one that is too small; this reduces the margin of error. Elevated blood pressure readings may also be obtained if the cuff is not applied evenly and snugly. A loose-fitting cuff needs a higher pressure within it to occlude the artery, and therefore higher readings are recorded on the mercury manometer.

Table 43–6. Clinical Methods of Recording Blood Pressure

Palpation
Auscultation
Ultrasound Doppler
Oscillometric
Flush

Palpation

A palpated blood pressure allows a quick assessment of the systolic pressure in a small infant and should be recorded initially, since attempts at measuring the blood pressure by auscultation are occasionally frustrated by the sometimes poor transmission of Korotkoff sounds in the infant and young child and by lack of cooperation. The disadvantage of the palpated pressure is that the palpated systolic figure is about 10 mm Hg lower than the intra-arterial pressure or auscultated pressure, and diastolic pressure is not obtainable.[86] Also, the diagnostically important pulse pressure is not obtainable except by manual estimation, as already described.

Auscultation

To obtain auscultatory blood pressure in a small child, use the small pediatric head, either bell or diaphragm, of the stethoscope. Excessive pressure damps the Korotkoff sounds and is a common error in recording blood pressure of the infant or child. The systolic pressure is recorded as the first audible Korotkoff sound, while the diastolic pressure should be recorded both when the Korotkoff sounds become muffled and when they disappear. While muffling may be the most accurate point of documenting diastolic pressure, it is often difficult to appreciate in a small infant.

The principles of cuff application and cuff size also apply to the lower limb for the recording of blood pressure. Therefore the cuff should cover two thirds of the thigh, leaving the popliteal fossa available for palpation, asucultation, or the positioning of a Doppler ultrasound transducer. It is ideal to place the subject in the prone position for leg blood pressure, but infants may not tolerate this.

Doppler Method

The Doppler ultrasound technique has been used effectively for almost 15 years, and the accuracy of the values obtained have been substantiated in many clinical studies, particularly by Steinfeld and colleagues.[87] With the transducer placed over the artery, arterial wall oscillations are transformed into an audible signal at the moment the intrabladder pressure drops below the peak intravascular pressure. The sound terminates when the intrabladder pressure dips below the end-diastolic pressure. The systolic pressure recorded in this manner is very accurate; however, the diastolic pressure is not as reliable.

Oscillometric Method

More recently, oscillometric methods have been developed.[88] Special cuffs are available to complement the system, which has many advantages, in particular in the small infant. Systolic, diastolic, and mean arterial pressures as well as heart rate are digitally

displayed. Recordings can be automatically repeated at frequent intervals if required. Examiners should be wary of technical artifacts with this method. The mean is the most accurate; systolic and diastolic are calculated.

Flush Technique

While the flush technique is rarely used currently, it still has a place and can be very valuable as a means of obtaining blood pressure in the infant with suspected coarctation of the aorta. Many times, both auscultated and palpated pressures are not obtainable in the lower limb in the presence of coarctation, and more sophisticated equipment may not be available. The pressure reading obtained by using the flush technique is closer to the mean arterial pressure than to peak systolic pressure. It does, however, allow a comparison between upper and lower limbs. The principle of the technique is similar to that already described for cuff application. Thereafter the limb is elevated, and an elastic bandage is applied from the fingertips or toes proximally to eliminate blood from the skin capillaries and veins and to blanch the distal forearm and hand or lower leg and foot. With the bandage still applied, the blood pressure cuff is inflated at least 20 or 30 mm Hg above the expected systolic pressure; and with the cuff inflated, the bandage is removed. The distal limb should now be white. The pressure in the cuff is decreased by 2 to 3 mm Hg per second, and the pressure at which the first blush appears in the limb is recorded as the blood pressure. The reading may be 10 to 30 mm Hg lower than that obtained by the auscultatory method.

Jugular Venous Pressures

Elevation of the jugular venous pressure indicates elevated right atrial pressure or increased right ventricular preload. Patience and experience are required to obtain maximum information from the venous pulse wave. In the small infant, the liver size is a more reliable indicator of systemic venous congestion. The jugular venous pressure is difficult to assess in the young infant because of the short neck. Also, there appears to be a greater compliance to the venous system in infants, so even in the presence of congestive cardiac failure, the right atrial pressure may not be significantly elevated and then only as a terminal event.[89] Venous pulsation in the neck is recognized and differentiated from the arterial pulsation in the following ways:

(1) the venous pulse has a multiple wave form with A, C, and V waves and with X and Y descents;
(2) height of the venous pressure varies with respiration, decreasing during inspiration;
(3) the venous pulse is easily obliterated by light pressure just above the clavicle;
(4) the pulsation is usually not palpable; and
(5) the level of pulsation changes with variation in posture.

The timing of the venous pulse waves can be facilitated by palpating the apex beat or auscultating the heart sounds.

The A wave is due to atrial contraction and is therefore presystolic. The C wave occurs at the onset of ventricular systole and is related in part to conduction of the carotid pulse and also to a wave initiated by displacement of the tricuspid valve during the onset of ventricular systole. The V wave marks the end of ventricular systole and occurs approximately with the dicrotic notch on a carotid pulse tracing. The X descent occurs during ventricular systole as the right atrioventricular valve is drawn from the right atrial cavity, reducing the right atrial pressure in the process. The Y descent occurs during rapid ventricular filling.[89]

It is not easy to evaluate the jugular venous pulse in an infant or child, and it takes practice to perfect the skill. To assess the jugular venous pressure, place or hold the subject upright at 45° to 90°; if venous pulsation is visible in the external jugular vein at or above the level of the suprasternal notch, then there is elevated right atrial pressure.[89] To analyze the venous pulse in more detail, the patient should be positioned in such a way that the maximum amplitude of the pulse can be visualized. This may be at 30°, 45°, 60°, etc. The height of the jugular venous pressure is measured as the vertical height above the sternal angle, or Louis' angle.[89]

Prominent A waves related to atrial contraction will be evident in tricuspid atresia or stenosis and indeed in any lesion causing elevation of right ventricular end diastolic pressure, e.g., severe pulmonary valve stenosis. A regurgitant wave or prominent V wave seen during ventricular systole may be caused by tricuspid insufficiency. Differentiating a prominent A wave from a V wave or regurgitant wave can be very difficult to do accurately in the infant or in any patient with tachycardia. Another easily identifiable pattern is that associated with complete AV block in which there are variable A waves and intermittent cannon waves. The cannon wave, a sudden and transient increase in jugular venous pressure, occurs when right atrial contraction takes place during ventricular systole and therefore against a closed right atrioventricular valve.

Marked distension of the jugular veins may be noted in the presence of constrictive pericarditis, and the pressure may increase rather than decrease during inspiration (Kussmaul's sign). Another cause of very prominent venous pulsation in the neck and sometimes an associated thrill is a large cranial arteriovenous malformation. Unilateral distension may be associated with a localized arteriovenous fistula. Distended nonpulsatile jugular veins may be a sign of superior vena caval obstruction, e.g., following intraatrial repair of transposition of the great arteries.

Edema

Edema (Greek: "oideo" = swell) of the extremities, which is a frequent feature of systemic venous congestion in adults and older children, is rarely seen in infants. When present, periorbital swelling may be evident. Rarely, puffiness of the hands and feet is also seen. If there is marked edema of the hands and feet, then a renal cause should be sought and hypoalbuminemia excluded. Nonpitting edema or lymphedema is found in the neonate with Turner's syndrome.

In the absence of obvious edema, an inappropriate increase in weight may indicate fluid retention in the small infant.

Hepatomegaly

The hallmark of systemic venous congestion in the infant is hepatomegaly. The abdomen should be examined with warm hands and with a gentle technique. The normal liver in the infant is soft and may be palpable 2 to 3 cm below the right costal margin. This decreases with age to approximately 2 cm at 1 year of age and 1 cm by 4 or 5 years. The position, the size, and the consistency of the liver should be noted. A liver in the right hypochondrium indicates normal visceral situs, while a left-sided liver suggests visceral inversion. In stating the size of the liver, it should be understood that the measurement is taken at the midclavicular

line where it crosses the ninth costal cartilage. When the liver is midline, situs ambiguous is present, and the assessment of size is measured from the subxiphoid position.

In the presence of right heart congestive failure or a generalized increase in circulating blood volume, the liver is not only enlarged, and therefore palpable more than 2 to 3 cm below the right costal margin, but it is also firm, with a rounded contour to the upper surface, which may make the edge more difficult to define. However, the edge can be defined by gentle backward pressure while allowing the descent of the diaphragm to press the edge against the examining fingers or thumb. Using the medial border of the thumb to feel the liver edge in a small infant is a useful and acceptable technique. Remember that the enlarged liver may also be tender, and undue pressure may distress the infant. Many beginners in medicine exert excessive pressure in attempting to palpate the liver. A pulsatile liver suggests tricuspid regurgitation or another reason for increased right atrial pressure (e.g., tricuspid atresia with small foramen ovale). In assessing the liver and spleen, therefore, not only should the size be noted but also the texture and the consistency. A hard liver of 2 cm may be more indicative of serious pathology than a soft liver that is palpated 4 cm below the right costal margin.

The span of the liver can be further confirmed by percussion. The upper margin may be depressed from the normal fourth intercostal space by hyperinflation of the lungs, creating the false impression of hepatomegaly when the abdomen is palpated. Percussion in the infant and child should be gentle and light. A heavy percussion technique not only gives less information but may also cause discomfort or pain to the infant, especially if the liver is enlarged and tender.

The spleen tip is frequently palpable under the left costal margin in the normal newborn. It is important to document this, since it excludes asplenia. On the other hand, if the spleen is significantly enlarged, this may suggest an intrauterine viral infection such as rubella as the cause of the cardiac lesion. In the older child with a congenital heart defect and a febrile illness, splenomegaly suggests possible endocarditis. It is uncommon to have significant enlargement of the spleen in isolated congestive cardiac failure.

In palpating the spleen, it should be remembered that the small infant's spleen may enlarge toward the left iliac fossa and therefore is more laterally positioned than in the older child.

In the presence of severe congestive cardiac failure, ascites may also be present and can be detected by dull flanks, shifting dullness, and a fluid thrill.

Pulmonary Congestion

In most cases, infants with congestive failure have no auscultatory findings in the lungs. In older children, fine rales may occur. Coarse rales at any age suggest pneumonia.

EXAMINATION OF THE HEART

Observe the shape of the chest for any asymmetry. Is the left precordial area bulging, suggesting a dilated right ventricle? Is Harrison's groove present, indicating a chronic decrease in pulmonary compliance? Harrison's groove is a depression along the sixth and seventh costal cartilages at the site of attachment of the anterior part of the diaphragm.[90]

Is there an increased anteroposterior diameter of the chest, perhaps related to chronic air trapping and hyperinflation of the lungs? Is there scoliosis, which may significantly alter the position of the standard landmarks on the anterior chest such as the apex beat?

The Apex Beat

The character as well as the position of the apex beat should be noted consistently, since this observation helps to assess ventricular hypertrophy and/or dilatation. In a young infant or a child up to four years of age, the apex beat is normally in the fourth intercostal space either at or inside the midclavicular line. A forceful apex beat in the normal location indicates either increased cardiac output or left ventricular hypertrophy without ventricular dilatation. When the left ventricle is dilated, the apex beat is displaced downward and inferiorly and is hyperactive.

An indistinct apex is found in association with right ventricular hypertrophy. In the presence of pronounced right ventricular dilatation, the precordium heaves, but the apex beat may be difficult to feel or localize.

Palpation

To get the most out of palpation of the anterior chest, use the most sensitive portion of the hand. For some, this is the palmar surface of the heads of the metacarpals, while for others it is the fingertips. Generally, the right ventricular impulse can be felt best with the hand resting on the precordium. In the young child with a thin chest wall, a slight impulse can be felt along the left sternal edge. A hypertrophied (but not dilated) right ventricle produces a distinct parasternal tap, while a dilated right ventricle (with or without associated hypertrophy) produces a parasternal lift.

The examiner identifies the apex impulse best with the fingertips. If the subject is old enough, search for the apex impulse in the upright position or, better yet, the standing position. A thin chest wall facilitates evaluation of the apex. Many physicians use the ambiguous term "point of maximum impulse" (PMI) to indicate the apex impulse. It is less confusing simply to use the term "apex impulse" if that is what one means. If the parasternal impulse is the stronger, one should so indicate. Most examiners locate the apex beat's interspace and relation to midclavicular or anterior axillary line. This is of course important, but the character of the apex beat also gives much valuable information. A very strong apex impulse, though normally formed, is associated with either of two cardiovascular conditions: increased cardiac output (the tachycardia of high fever, severe infection, anemia, anxiety, or immediately after exercise) or left ventricular hypertrophy. If the overactive apex beat is also displaced both downward and to the left, dilatation of the left ventricle (with or without hypertrophy) can be assumed.

Thrill

Very few physicians carrying out a cardiovascular physical examination overlook the search for a precordial, suprasternal, or carotid artery thrill. A thrill simply indicates a loud murmur. Some beginning examiners report a precordial thrill but only a faint grade 1 to 2 murmur. If the murmur is of low intensity, the examiner has probably felt a pulsation and not a thrill. It is interesting to identify a thrill, but an examiner who intends to listen over the heart and the carotid arteries will likely identify a prominent murmur. Missing a thrill during palpation is not critical to a correct evaluation of cardiac function and structure.

A thrill associated with aortic stenosis and pulmonary stenosis usually signifies an important obstruction, but so does a loud murmur. There is no such correlation with ventricular septal defect, since an easily palpable thrill may be present with either a small or a large defect. Sometimes the location of a thrill may be misleading. A thrill in the suprasternal notch to most examiners suggests aortic stenosis, but a thrill in that location may be transmitted to the aorta from a prominent thrill in the pulmonary trunk due to pulmonary valve stenosis or a large patent ductus.

Palpation of Heart Sounds

By palpation, an accentuated heart sound also may be felt, especially in the infant or young child in whom the chest wall is thin. The second heart sound in the pulmonary valve area can usually be felt if there is pulmonary diastolic hypertension. It can also often be felt in transposition (either dextro, i.e., true, transposition, or levo, so-called corrected, transposition), since the aortic valve in both types of transposition lies anterior to the pulmonary valve. A palpable first heart sound can often be felt in the presence of a hyperdynamic heart from any cause, including exercise or fever.

While it is interesting for the examiner to palpate heart sounds before listening to the heart sounds with a stethoscope, the loud sound or click is going to be heard, so overlooking a palpable sound, just as overlooking a thrill, is not critical to the functional and structural evaluation of the cardiovascular system.

Percussion

In the infant, percussion of the cardiac borders has very limited value. It is probably the relative increase in anteroposterior diameter of the chest or perhaps the often increased amount of fat tissue in the newborn's chest that damps the percussed difference between heart border and lung. It would be risky in the infant to depend upon percussion of cardiac borders to detect either cardiac dilatation or massive pericardial effusion. It really requires the combination of chest radiograph and ultrasound to be certain about it. In older children, if the left cardiac border by percussion extends beyond the apex beat, a pericardial effusion is suspected.

Percussion of the lungs, however, forms an important part of the examination and can be successfully carried out in the quiet infant. In the infant (as in older patients), chest percussion has to be carried out with the subject upright. Examiners often try to percuss the posterior chest with the infant prone on the examining table, but this does not work. Have the parent or nurse hold the infant upright both for percussion and for auscultation of the lungs.

Auscultation of the Heart

Expert auscultation of the heart first has to be learned, over a period of weeks to months, studying under an experienced instructor and having available a sizable number of subjects (patients) with a variety of normal and abnormal heart sounds and murmurs. Once mastered, the technique of hearing and correctly interpreting the auditory variants missing from the normal and abnormal heart must be practiced often for an examiner to remain skillful (Table 43–7).

When possible, every infant and child should be examined in both the supine and the standing posture. The older child should also be evaluated following light exercise, such as running in place. A subtle ejection click can be exaggerated, and a short diastolic murmur that may be difficult or impossible to hear at rest often becomes clearly apparent in one position and not in another. This is particularly true of the diastolic rumble in the tricuspid area in a child with an atrial septal defect (best heard supine) or the high-pitched decrescendo diastolic murmur of aortic regurgitation (best heard in the upright position).

Table 43–7. Components of Auscultation of the Cardiovascular System

Stethoscope
Use in each site:
Bell
Diaphragm
Short tubing (16–18 in.)
Use familiar (personal) and comfortable instrument
Auditory Conditions
Insist on quiet:
Patient
Parents
Attendants
Examining room
Adjacent areas
Areas to Examine Routinely
Primary aortic (2nd intercostal space, right sternal edge)
Pulmonary (2nd intercostal space, left sternal edge)
Tricuspid/2nd aortic area (4th intercostal space, left sternal edge)
Mitral/apex (5th intercostal space, midclavicular line or at apex if displaced)
Right and left infraclavicular area
Right and left axillae
Right and left interscapular areas (especially if pulmonary or aortic collaterals are suspected)
Right and left carotids (especially if thrill present)
Cranium (right and left temporal areas) (especially in newborn with heart failure)
Right and left lumbar region (especially if high blood pressure)
Abdominal aorta (especially if abdominal coarctation or aneurysm suspected)
Right and left femoral arteries (especially if evaluating wide pulse pressure)
Patient Position
Examine each valve area with patient:
Supine
Sitting
Standing (brings out click of mitral leaflet prolapse)
Squatting (to reduce murmur of aortic stenosis with hypertrophic cardiomyopathy and exaggerating or eliciting murmur of mitral regurgitation)
Effect of Respiration During Basal Conditions
Quiet, deep, unforced, continuous respiratory excursion
Deep-held inspiration, then expiration
Effect of Varying Cardiac Output
Basal (or quiet, resting) state
During increased cardiac output (exaggerates most murmurs and elicits some)
After exercise
After a large feeding in an infant

Conditions for Auscultation

Auscultation of sick infants in an intensive care unit can be difficult with so much extraneous noise in the environment such as the bleeps from monitors, the hum of the incubator, and the continuous sound of airflow in infants on continuous positive air-

ways pressure. It is therefore necessary to try to achieve as quiet an environment as possible.

It is very easy to be distracted by a loud murmur and ignore the quality and characteristics of the first and second heart sounds. As a consequence, valuable diagnostic information can be lost.

Table 43–8 outlines some causes and clinical significance of variation in the quality and timing of the first and second heart sounds.

The first heart sound was considered by Leatham to be produced by closure of the mitral and tricuspid valves.[91] In recent years, other investigators have demonstrated that the components of the first heart sound are produced by acceleration and deceleration phenomena within the left ventricle and that tricuspid leaflet apposition plays little part in the generation of the first sound.[92] Despite this, the traditional concept can be helpful in conceptualizing and teaching heart sounds.

While multiple components of the first heart sound are recordable by sensitive phonocardiograph equipment, only a single sound is audible at the apex and at the lower left sternal border in most healthy individuals. However, in many children and adolescents, when the heart rate is slow enough, two components are clearly heard. This physiologic splitting is heard better at the tricuspid area at the lower left sternal border than the apex, a result suggesting that there is indeed a tricuspid valve contribution to the first sound. If a split first sound is heard better at the apex, it may be that one component of the sound is an aortic ejection click, a manifestation of bicuspid aortic valve or noncalcific aortic stenosis.

The intensity of the first sound depends on the velocity of "leaflet closure" (more precisely, acceleration and deceleration of blood flow near the atrioventricular valves) and therefore on the rate of rise of the ventricular systolic pressure and the stroke volume. Any factor that increases the cardiac output, such as exercise, pyrexia, or anemia, will exaggerate the intensity of the first heart sound.

Mitral stenosis is the archetypical cause of a pathologic loud first heart sound. The sound is loud because the high left atrial filling pressure produces a greater acceleration of blood flow from atrium to ventricle, and with the onset of ventricular pressure, a very rapid deceleration of blood flow across the mitral valve occurs.

Congenital mitral stenosis for some reason lacks the characteristically loud first heart sound noted in acquired rheumatic mitral stenosis.

A decreased intensity of the first heart sound may indicate a prolonged PR interval, significant mitral regurgitation, reduced rate of rise of ventricular pressure, and reduced ventricular stroke volume from any cause.

Second Heart Sound

In infants and young children, the importance of an increased intensity of second heart sound in the evaluation of cardiac misfunction is often misinterpreted. The second heart sound is split in two thirds of infants by 16 hours of age and in 80% by the age of 48 hours.[52] But at a heart rate of over 100 beats per minute, physiologic splitting is hard to detect by auscultation; often, the closely split heart sound may be audible as a single sound.

Splitting of the second heart sound is audible when the aortic and pulmonary components are separated by 20 ms or more. In the normal individual, splitting is best detected in the second left intercostal space at the left sternal edge. Respiratory variation of splitting should be assessed during quiet ventilation.

Splitting of the second heart sound depends upon a different impedance in the systemic and pulmonary vascular beds.

Curtis and associates have demonstrated that physiologic splitting with delayed closure of the pulmonary valve is primarily the result of a fall in pulmonary vascular impedance during inspira-

Table 43–8. Heart Sounds

Sound	*Variation*	*Example*
S_1	decreased	depressed ventricular ejection rate and volume, e.g., prolonged PR interval
S_1	increased	increased cardiac output, e.g., exercise, fever, excitement, mitral stenosis
S_2	single, increased	transposition tetralogy of Fallot with marked overriding of aorta pulmonary hypertension truncus arteriosus
S_2	single, decreased	typical tetralogy of Fallot
S_1 and S_2	decreased	decreased ventricular ejection rate and volume (low cardiac output) large pericardial effusion
S_2	splitting, wide and usually "fixed"	atrial septal defect right bundle branch block
S_2	splitting, wide but moves with respiration	pulmonary stenosis ventricular septal defect or patent ductus arteriosus with large shunt idiopathic dilatation of pulmonary artery
S_2	splitting, reversed	Wolff-Parkinson-White syndrome (some cases) left bundle branch block left ventricular failure

tion.[93] There is only a minor contribution from an increase in the duration of right ventricular systole and earlier aortic valve closure during inspiration. The aortic and pulmonary closure sounds occur at the incisurae of their respective pressure curves. These incisurae are separated from a corresponding point on the ventricular pressure trace by an interval denoted as "hangout." In the normal systemic circulation, this interval is less than 20 ms, while the duration of this interval in the normal pulmonary circulation is considerably wider, varying from 33 to 89 ms. The fall in pulmonary vascular impedance with inspiration increases this hangout interval.

In normal children lying supine, slight splitting of the second heart sound may persist during expiration. In the upright position, however, the normal second heart sound usually becomes single. Persistent expiratory wide splitting of the second heart sound in the upright position rarely occurs normally; it is a common sign of atrial septal defect, complete right bundle branch block, or Wolff-Parkinson-White syndrome.

In the small infant and in many patients with a rapid heart rate, it is more important and feasible to recognize that wide splitting is present than to attempt to hear respiratory variation in S_2. Splitting theoretically indicates that there are two functioning semilunar valves; however, one may inexplicably hear splitting in truncus, or even after tetralogy of Fallot repair in which the pulmonary valve has been totally excised.

The second sound is single and increased in intensity in transposition of the great arteries of tetralogy of Fallot. In transposition, the aorta is anteriorly placed, and the pulmonary valve closure sound is inaudible in its posterior position. In the type of tetralogy of Fallot in which there is extreme overriding of the aorta, the aortic valve closure is loud. A single loud second heart sound may be found in association with pulmonary artery diastolic hypertension, especially when pulmonary vascular resistance is at systemic level.

A loud pulmonary valve closure sound indicating pulmonary hypertension should always be interpreted in relation to the physiologic mechanisms that create elevated pressure (P), i.e., increased blood flow (F) or increased vascular resistance (R), ($P = F \times R$). Simply stating that a patient has pulmonary hypertension is incomplete. The same intensity of pulmonary valve closure may be heard with low pulmonary vascular resistance, a large left-to-right shunt, and therefore a potentially correctable defect as is heard in the child with reduced blood flow, high pulmonary vascular resistance, and an uncorrectable anomaly. In the latter type of child, the murmur becomes short and of low intensity and provides the clue to fixed pulmonary vascular obstructive disease.

In infants and children with mild pulmonary valve stenosis, there is exaggerated splitting of the second heart sound. A normal pulmonary valve closure sound in the presence of other findings indicative of pulmonary valve stenosis suggests that the degree of obstruciton is mild, while an inaudible or very diminished pulmonary sound usually indicates severe obstruction.[26]

Fixed splitting of the second heart sound, i.e., a less than 20-ms variation in splitting during the respiratory cycle, is a characteristic finding in atrial septal defects and is of great diagnostic importance in children with these defects. With a large defect and a large left-to-right shunt, fixed splitting persists in both supine and sitting positions. The cause of fixed splitting in association with an atrial septal defect was once considered to be prolongation of right ventricular systole, which caused a delay in closure of the pulmonary valve. However, studies by Shaver and colleagues demonstrated that prolongation of right ventricular systole contributes only a minor component of the overall duration of the splitting. The major contribution is related to an increase in the capacitance of the pulmonary vascular bed and therefore a fall in pulmonary vascular impedance.[94] The fall in pulmonary vascular impedance causes a prolongation of the hangout interval before pulmonary valve closure. There is no significant change in the hangout interval in the systemic circulation. In this setting, the respiratory changes in right heart volume do not alter the hemodynamics, and therefore fixed splitting occurs.[95]

Expiratory splitting of the aortic and pulmonary components is also found in idiopathic dilatation of the pulmonary artery and in patients with mild pulmonary stenosis.[96] In both instances, the dilated pulmonary arteries increase the capacitance of the pulmonary vascular bed, delaying pulmonary valve closure (or cessation of forward pulmonary blood flow) significantly beyond the end of right ventricular systole.

As the capacitance of the pulmonary vascular bed decreases from any cause, the degree of splitting lessens. This is noted in normal people with age; 45% of subjects over 40 years of age have inspiratory splitting of the second sound of only 20 ms or less, rendering the second sound single.[93] A decrease in the capacitance also occurs in association with an increase in pulmonary vascular resistance, giving rise to a single second heart sound in the pulmonary area. In the newborn, this is a constant feature with persistent fetal circulation. Also in infants and children with a large ventricular septal defect or patent ductus arteriosus, as pulmonary resistance increases and the degree of left-to-right shunting is diminished, the splitting of the second heart sound becomes less and ultimately single as the process progresses toward Eisenmenger's syndrome.

Splitting of the second heart sound therefore needs to be considered in terms of the pulmonary vascular resistance, the capacitance of the pulmonary vascular bed, and the right ventricular function.

Reversed splitting of the second heart sound in children is rare but may occur in association with left bundle branch block, Wolff-Parkinson-White syndrome, or left ventricular failure.[96]

Third Heart Sound

Third heart sound is a low-frequency transient sound of 20 to 70 cycles per second that occurs during rapid filling of the ventricles during early diastole. While the third heart sound can be recorded by sensitive phonocardiography, trained and experienced examiners can hear this physiologic sound in healthy children. The intensity of the sound can be exaggerated by exercise or any factor that increases cardiac output. However, a very rapid rate may obscure it. The third sound is audible and prolonged, producing a diastolic flow murmur in patients with increased volume of blood flow from atrium to ventricle. In the left ventricle, it occurs in ductus arteriosus, ventricular septal defect, or mitral regurgitation. Over the tricuspid area, an exaggerated third heart sound or diastolic flow murmur can be heard in atrial septal defect in which the pulmonary blood flow is at least twice the systemic flow.

The exaggerated third heart sound or middiastolic flow murmur is a difficult one to learn how to hear. It is short and low-pitched,

and even experienced examiners must make a special effort to listen for it. But it is highly important in estimating the volume of a left-to-right shunt or the severity of mitral regurgitation.

This murmur produces a gallop rhythm and resembles something like "Ken-tuck'-y." It is sometimes mistaken for the gallop of heart failure. However, the so-called heart failure gallop is an audible fourth sound, the result of raised ventricular end-diastolic pressure.

Fourth Heart Sound

An audible fourth heart sound (a low-frequency transient sound of 20 to 50 cycles per second), as distinct from the third heart sound, is nearly always pathologic and indicative of altered ventricular compliance. This sound follows atrial contraction and, like the third heart sound, is caused by vibrations within the ventricular myocardium. A fourth sound is uncommonly heard in children with heart disease but may be noted in those with hypertrophic cardiomyopathy. A fourth heart sound may also be noted in children with severe systemic hypertension or in those with a congestive cardiomyopathy, particularly in association with endocardial fibroelastosis.

Ejection Sounds

The ejection click is a snappy high-frequency sound and therefore best heard with the diaphragm of the stethoscope. It occurs during the early ejection phase of ventricular systole. Typically, it is associated with pulmonary or aortic valvular obstruction, but it may also be generated within a dilated aortic root or pulmonary trunk. An aortic ejection click occurs in truncus arteriosus and may be generated either by a degree of thickening and doming of the valve leaflets or by vibrations within the dilated truncal root. It can similarly be heard in pulmonary trunk atresia with ventricular septal defect. The ejection click is often mistaken for a loud first heart sound. An ejection click in association with pulmonary valve stenosis is heard in the pulmonary area and along the left sternal border. In mild pulmonary stenosis, the click is brought out by exercise. It is louder during quiet inspiration and may reduce or disappear during expiration. The ejection sound, while usually present in association with severe pulmonary valve stenosis, may be difficult to hear, since it moves earlier in systole and may appear to fuse with the first heart sound.

Probably the high rate of rise of elevated right ventricular pressure (RVDP/DT) forces the stenotic valve leaflets up so rapidly that a snap or click becomes audible like the pop of a sail when the wind suddenly balloons it out. The click usually disappears in severe valve pulmonary stenosis with decompensation when the rate of pressure rise has decreased.

Aortic ejection clicks are best heard at the apex and in the secondary aortic area left lower sternal border at the fourth space rather than in the so-called primary aortic area at the right second intercostal space. An isolated aortic ejection click suggests a bicuspid aortic valve, which occurs in approximately 1% of the population. The aortic click varies less with respiration than the pulmonary click. An aortic ejection click typically occurs with noncalcified aortic valve stenosis but not in subvalve or supravalve aortic stenosis.

Midsystolic Click and Mitral Leaflet Prolapse

The midsystolic click of mitral leaflet prolapse is best heard at the apex or, in triscuspid leaflet prolapse, at the left lower sternal border, fourth space. This sound may be heard in either the supine or the standing position or both, but sometimes only with the patient standing. A late crescendo mitral valve murmur may or may not accompany the click. Squatting exaggerates the murmur, but this position has a variable effect on the click.

Click Associated with an Aneurysm of the Ventricular Septum

Many infants with ventricular septal defects form a wind sock of tissue or aneurysm that develops in the process of spontaneous closure or reduction in size of ventricular septal defect. During ventricular systole, this aneurysm bulges into the right ventricle, producing an early systolic click. This click is best heard at the mid-left sternal border in the third left intercostal space and with the infant or child sitting at approximately 45°.[97] It is indistinct, however, and a difficult sound to learn how to hear.

Murmur

A murmur is the most frequent reason for referral of a patient for cardiac evaluation. However, reliance on hearing a murmur is not a very sensitive or specific screening method for case detection, especially in infants. Either benign or serious heart disease, including congenital and acquired types, often occurs in the absence of a murmur. In addition, anomalies that create a characteristically loud distinct murmur such as aortic valve stenosis may, in the infant with congestive failure, produce no murmur.

Too great a reliance on the detection of a murmur has been the cause of significant delays in recognizing congenital heart disease even when the other signs and symptoms of congestive cardiac failure are already evident.[8] Two of the most frequently missed diagnoses during childhood are atrial septal defect and coarctation of the aorta. The diagnosis of the former depends more on the wide splitting of S_2 than on the variable murmur, which may be too faint to attract the unsuspecting examiner's attention. Coarctation may be missed in infancy and early childhood if one is examining only for heart murmurs to detect heart disease. While the adolescent patient with coarctation usually has a well-developed murmur, the younger patient often does not. A murmur is nevertheless an important physical sign and helps the physician to suspect heart disease and sometimes to make an anatomical diagnosis and even to assess severity. It is of interest, if not diagnostically important, to learn the age of the patient when a physician first heard a murmur. The murmur of small ventricular septal defect may be heard at birth, but this is not the case with large nonrestrictive ventricular septal defect, since the murmur in this instance first appears after pulmonary vascular resistance falls at 2 to 6 weeks of age. In the normal full-term newborn, pulmonary resistance starts to fall promptly within the first few breaths; presumably, this occurs also in small interventricular communication. In fact, the infant with a ventricular septal defect is often discharged from neonatal care with an apparently normal heart only to present at 1 month of age with a typical pansystolic harsh murmur at the lower left sternal border, often with signs of pulmonary congestion and dilated heart.

The age of first appearance of a murmur to a physician was recorded in 166 patients, each of whom ultimately developed a murmur by the time of referral to the cardiac clinic at Texas Children's Hospital. In approximately 26%, the murmur was first heard in the first two weeks of life; but in more than one third of

the patients, the murmur was not heard until after the infant was three months of age. The author suggested that the frequent late appearance of the murmur no doubt accounted for some of the difficulty in the early diagnosis of congenital heart disease.[98] If a child has been examined by a pediatrician during the first two years of life and a murmur is heard for the first time after that age, the probability is that the murmur is innocent.

There are 11 ways to describe a murmur (Tables 43–9 and 43–10). Murmurs are usually graded on the basis of their intensity. Every junior medical student knows the grading system from I through VI, and it is unnecessary to repeat it in this work. Intensity grading is not precise, but no harm is done if one examiner calls the murmur a Grade III and the next a Grade II. But trained examiners seldom differ by more than one grade. The point is to give an approximate indication of how loud a murmur is, and this has practical value. In some malformations, the murmur changes in loudness from one time to the next. For example, in tetralogy of Fallot, patients may on some days inexplicably develop a reduction in the volume of blood going from right ventricle to pulmonary artery with the result that a greater amount of blood traverses the ventricular septal defect into the aorta. There results a sharp reduction in the murmur intensity or even a complete disappearance. It is, of course, the pulmonary stenosis rather than the right-to-left ventricular shunt that produces the murmur in tetralogy of Fallot.

In nonrestrictive ventricular septal defect with a large left-to-right ventricular shunt, one characteristically hears a very loud Grade III, IV, or V murmur, depending upon the amount of blood turbulence from the shunt. Some infants with this defect gradually develop pulmonary vascular obstructive disease, the left-to-right shunt decreases and so does the intensity of the murmur. In fully developed Eisenmenger's syndrome, when all the ventricular shunt becomes right-to-left, the systolic murmur virtually disappears. There are many other reasons why grading the intensity of the murmur is important, but students sometimes exert too much concern over whether a murmur is Grade III or IV. Besides, a murmur can increase in grade by at least one level in the presence of a transient increase in cardiac output from fever or the like.

Attention to the approximate vibrations of a murmur in terms of approximate cycles per second helps in both the anatomic diagnosis and the hemodynamic evaluation. Examiners in training soon learn to recognize a certain defect by its characteristic sound. For example, the harsh, rough, long plateau murmur of ventricular septal defect contains a mixture of high-pitched and low-pitched sounds and is quite different from the long plateau but the pure high-frequency sound of mitral valve regurgitation. Physicians

Table 43–9. Description of a Murmur

1. Intensity (Grades I–VI)
2. Phase (systole, diastole, continuous)
3. Shape (crescendo, decrescendo, "diamond," plateau)
4. Timing (early, mid, late)
5. Length (short, medium, long, pan)
6. Pitch (low, medium, high)
7. Quality (vibratory, harsh, rumbling)
8. Location of maximum intensity
9. Radiation of murmur
10. Effect of maneuvers (inspiration, standing, squatting)
11. Eponym (Still's, Austin-Flint, Carey Coombs, Graham Steell)

Table 43–10. Several Eponyms Associated with Cardiac Murmurs

Eponym	*Description*
Austin Flint murmur	Dr. Austin Flint of New York described this finding while on the faculty of the Charity Hospital in New Orleans. This was a low-frequency diastolic "blubbering" murmur at the cardiac apex caused by vibration of the anterior mitral leaflet in cases of aortic regurgitation.*
Hodgkin's murmur	The famous Thomas Hodgkin of Guy's Hospital in London published a clinical description of aortic regurgitation several years before Corrigan. Some still refer to the diastolic decrescendo murmur of aortic regurgitation as the Hodgkin's murmur, although this eponym is rarely used in the United States.†
Carey Coombs murmur	Dr. Carey F. Coombs of Bristol was one of the first physicians to have formal training in both cardiology and pediatrics. He described a middiastolic, apical, rumbling murmur in the early phases of acute rheumatic fever in patients with mitral regurgitation.‡ He thought that this murmur was caused by edematous mitral leaflets from the rheumatic inflammation, but a similar middiastolic murmur can be heard in congenital and myxomatous mitral regurgitation cases.
Graham Steell's murmur	A high-frequency diastolic decrescendo murmur in the pulmonary area was described by Dr. Graham Steell of Manchester due to pulmonary hypertension from rheumatic mitral stenosis.§ A similar pulmonary insufficiency murmur can be found in cases of severe pulmonary hypertension from other causes, such as primary pulmonary hypertension.
Gibson murmur	The continuous roaring ("train-in-the tunnel") murmur of a large patent ductus was described by Dr. Gibson at the turn of the century.‖ The eponym is used in some older publications.
Still's murmur	This common lower left sternal border, vibratory, musical systolic murmur is described in Chapter 109 in greater detail. Dr. George Frederick Still of Great Ormond Street Children's Hospital described this murmur in the early 1900s.¶

*Flint, A.: On cardiac murmurs. Am. J. Med. Sci., *44*:29, 1862.

†Hodgkin, T.: On the retroversion of the valves of the aorta. London Med. Gaz., *3*:433, 1829.

‡Coombs, C.F.: Rheumatic myocarditis. Q. Med. J., *2*:26, 1908.

§Steell, G.: The murmur of high pressure in the pulmonary artery. Med. Chron., *9*:182, 1888.

‖Gibson, G.A.: Persistence of the arterial duct and its diagnosis. Edinburgh Med. J., *8*:1, 1900.

¶Still, G.F.: Common Disorders and Diseases of Childhood. London, Frowde, Hadder and Stoughton, 1915.

develop an ear for the distinctive quality, pitch, shape, and duration of a certain murmur in much the same way that musicians learn to distinguish between an oboe and an English horn or naturalists learn the calls of different birds. Many new students in clinical medicine assume at first that they are tone deaf when they cannot hear, much less correctly identify, certain sounds when the problem is simply a matter of learning the sound with supervising faculty to guide them. One cannot successfully read about the quality of a murmur and then independently proceed to recognize it in a patient.

No one forgets to examine the heart with a stethoscope, but in the newborn infant with pulmonary and systemic venous congestion and a dilated heart, the physician should always listen over the cranium and the liver. A continuous murmur in these areas would suggest that the cause is arteriovenous fistula. Of course, not all cranial bruits are pathologic. Benign bruits not arising from fistulae can be heard in about 15% of normal children under 5 years of age.[99]

While the classical cause of a continuous murmur is the persistent ductus arteriosus, the typical murmur may not become evident in the full-term infant until after the newborn period or, in rare instances, much later in the first year of life. On the other hand, in the preterm infant with a functionally important patent ductus, one can hear a continuous murmur in only one third of the patients, a murmur confined to systole in approximately 60%, and absence of murmur altogether in the remaining 10%.[100]

Properly carried out, the history and physical examination can give the experienced examiner a great deal of information about the functional and sometimes the structural abnormalities of the cardiovascular system. Examiners who are convinced of the value of the history and physical examination do the examination the best. But one has to adhere to a strict protocol pertinent to each individual patient. Infants and children respond to patience and gentleness, and physicians must be prepared to take as much time and care with a clinical assessment as with evaluation of the hemodynamic and imaging data obtained at cardiac catheterization.

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CHAPTER 44

Noninvasive Diagnostic Methods: Plain Radiographic Diagnosis of Congenital Heart Disease

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CARDIAC EVALUATION BY RADIOGRAPHY

History

Early radiologic methods of cardiac evaluation consisted of chest fluoroscopy and radiographic studies. Fluoroscopic examination of the heart was considered an indispensable part of the evaluation. Relying solely on radiographic studies was as negligent as omitting fluoroscopy in the evaluation of gastrointestinal disorders. To be examined, the child was put in either a supine or upright position (depending upon age and cooperation), and careful fluoroscopic attention was given to diaphragmatic motion, pulmonary aeration, cardiac pulsations, and the pulsations of the main pulmonary arteries in the hilar regions. Then the patient would be turned 45° into a right anterior oblique position and then into approximately 60° in the left anterior oblique position. This was done to evaluate anterior and posterior borders of the heart and to identify, if possible, the size of the pulmonic and aortic windows. This procedure would be accompanied by a swallow of flavored liquid barium or barium paste. (The addition of chocolate syrup to the barium improved its taste.) After the fluoroscopic examination, radiographs were obtained in the anteroposterior (AP) or posteroanterior (PA) position, depending on the patient's age, as well as a lateral radiograph plus right and left oblique views of approximately the same angulation as the fluoroscopic studies.[1] Each of these radiographs was made following additional barium ingestion.

The introduction of image amplification fluoroscopy enabled physicians to carry out the fluoroscopic studies in a lighted room and to observe cardiac and hilar pulsations to better advantage. Increased amplitude of pulmonary artery pulsations (hilar dance) indicative of increased pulmonary blood flow was easily seen after the introduction of image amplification fluoroscopy. Prior to image amplification fluoroscopy, radiologists had to wear red goggles or sit in the dark in order to accommodate their eyes to the peripheral vision necessary for fluoroscopy. Soon it became apparent that fluoroscopy added little additional information to that obtained by the radiographic studies and was associated with a great deal more radiation than desirable. The damaging effects of radiation, both by diagnostic methods and especially following atomic detonations, produced enormous concern in the general population as well as among medical practitioners. This concern was especially directed to infants and children. Although the introduction of the image amplifier greatly reduced the amount of fluoroscopic radiation, fluoroscopy for routine study of the heart was proven unnecessary. However, because of the intensity of its image, it provided a method for cine and video recordings of angiocardiography. Today, fluoroscopy of the heart independent of catheterization is rarely carried out. But it is still useful when evaluating diaphragmatic excursion postoperatively when phrenic nerve injury is suspected.

What's in an X Ray?

In most cases, cardiac pathology is reflected in an abnormal chest x ray result. However, many serious cardiac abnormalities are not excluded by a normal x-ray film of the chest. Chest radiographs of the infant with tetralogy of Fallot and the adult with coronary disease may be strikingly normal. Another inconsistency in the requisition is a request to determine if there is cardiac hypertrophy. A measurement of hypertrophy is determined by elec-

trocardiography or echocardiography. Cardiac dilatation must be present in order to produce cardiomegaly either generally or in regard to a specific chamber.[2,3] For example, the left atrial myocardium may quadruple in thickness without altering cardiac size, and the left ventricle may double its wall thickness without appreciably changing cardiac dimension on plain films.[4]

RADIOGRAPHIC TECHNIQUE AND AMOUNT OF RADIATION

Although many restraints are available for immobilizing infants during the x-ray examination, the simplest and most practical method is to have a parent or aide (protected with an apron) hold the infant supine. The infant's elbows must be held against the ears to maintain the head in a straight position. Any head deviation results in rotation of the chest and an unacceptable AP view. The shorter tube film distance (36 to 40 in.) of a supine film does not produce the magnification seen in larger patients, in whom a 6-foot distance is required. No effort is made to keep the infant from crying, thereby enabling the technician to make the required exposure at the peak of inspiration. Gonadal shielding is imperative in all cases. A minimum of $1/60$ of a second of exposure is necessary for an acceptable radiograph; in order to have consistently good images, exposure times of at least $1/100$ of a second are preferable to avoid motion artifacts from respiratory movement and cardiac pulsations. The diaphragm should be at the level of the posterior portion of the eighth rib (or lower) to verify that an inspiratory film was obtained. Normal variations including pectoral muscle shadows, expiratory phase with high position of the diaphragm, and crowding of vascular markings should be considered in evaluating the film quality. The ability to see the thoracic spine through the mediastinal shadow in the frontal projection indicates the desired degree of penetration. Portable radiographs using condenser discharge equipment are useful for quality portable studies in the intensive care units, as well as in postoperative recovery rooms.

The approximate entrance skin dose in a small infant receiving one chest x ray is less than 10 mR over the anterior chest wall and less than 1 mR to the pelvis area.[5,6] However, the pelvis should be protected, not only during examinations in the x-ray department, but also with portable studies. To place these doses in perspective, it is notable that the annual exposure for an individual at sea level from natural radiation sources is 100 mR. Occupational workers should not exceed 5000 mR/year to the lens of the eye.

NORMAL RADIOGRAPHIC ANATOMY OF THE HEART

Infancy

It may be very difficult to evaluate accurately heart size in young infants if the thymus is large. A large thymus may completely envelop the cardiac silhouette in the frontal projection, making accurate measurements and establishment of a cardiothoracic ratio impossible. In addition, an infant's inability to hold his/her breath voluntarily in inspiration frequently results in radiographs with the diaphragm at a high level, producing an increase in the cardiothoracic ratio and crowding of the lung markings. The infant's thoracic cage is also wider than it is deep, as compared to the opposite dimensions in an older child. An acceptable inspiratory radiograph is one in which the diaphragm is at the level of the eighth rib posteriorly, or the sixth rib anteriorly. Because of the thymus and alterations in degrees of inspiration, the "cardiothoracic" ratio may be as much as 70% in an infant with a normal heart. The cardiothoracic ratio is the ratio of the largest transverse dimension of the heart to the widest intercostal diameter of the chest. Fluoroscopy may be helpful in identifying the thymus by showing the angle of the thymus when the patient is rotated into oblique positions and by demonstrating changes in configuration of the thymus with inspiration and expiration. In addition, the thymic "wave sign" usually can be identified on AP chest radiographs.[7] This sign consists of indentations on the lateral border of the thymus by the costal cartilages.

The thymus gradually reduces in size, and during the latter part of infancy and by the end of the second year (or the beginning of the third year) of life, the cardiac configuration usually resembles that of the older child. However, thymic tissue may persist during the first few years of life and should not be mistaken for an abnormal mediastinal mass. The use of steroids to "shrink" the thymus in order to evaluate the heart configuration or size is not indicated. Repeat chest radiographs in order to obtain a better inspiratory study are also rarely necessary. If the infant has pneumonia or congestive failure, it is more difficult for an x-ray exposure to be made in expiration since the tachypnea accompanying these conditions may guarantee a low position of the diaphragm. X-ray exposures made in cardiac diastole may suggest cardiomegaly but, again, other methods of cardiac evaluation are helpful for further assessment.

Childhood

Because of the variation of the mediastinal silhouette in infants, the description of the radiographic anatomy does not become consistent until later childhood. In order to demonstrate radiographic anatomy, AP (or PA) and lateral views of the chest as well as oblique views are necessary.

In the frontal projection (Fig. 44–1), the right cardiac border is the right atrium. The lower left cardiac border is normally the left ventricle. Above this is a normal convexity, the undivided portion of the pulmonary artery. The convexity above this is the aortic arch, which displaces the trachea slightly to the right. A right aortic arch is identified on the PA view as a fullness in the right superior mediastinum with displacement of the trachea to the left. The left atrial appendage contributes to the left heart silhouette between the pulmonary artery and left ventricle. But the atrial contour blends with the left ventricle and is distinct only when the atrium is dilated.

In the right anterior oblique (RAO) view, the right side of the patient's chest is against the cassette with the left side turned 45° from the flat surface of the cassette (Fig. 44–2). This position can be recognized by seeing the cardiac contour extend to or close to the chest wall anteriorly. The anterior chamber is the right ventricle and the convexity above this is the pulmonary artery; posteriorly the inferior shadow is the right atrium and above this, the left atrium. If the esophagus is outlined with contrast material, an indentation produced by a normal left aortic arch will be identified. Below this, an indentation by the left bronchus frequently is visible. The main advantage of this view is a demonstration of left atrial enlargement. When the left atrium enlarges, it extends pos-

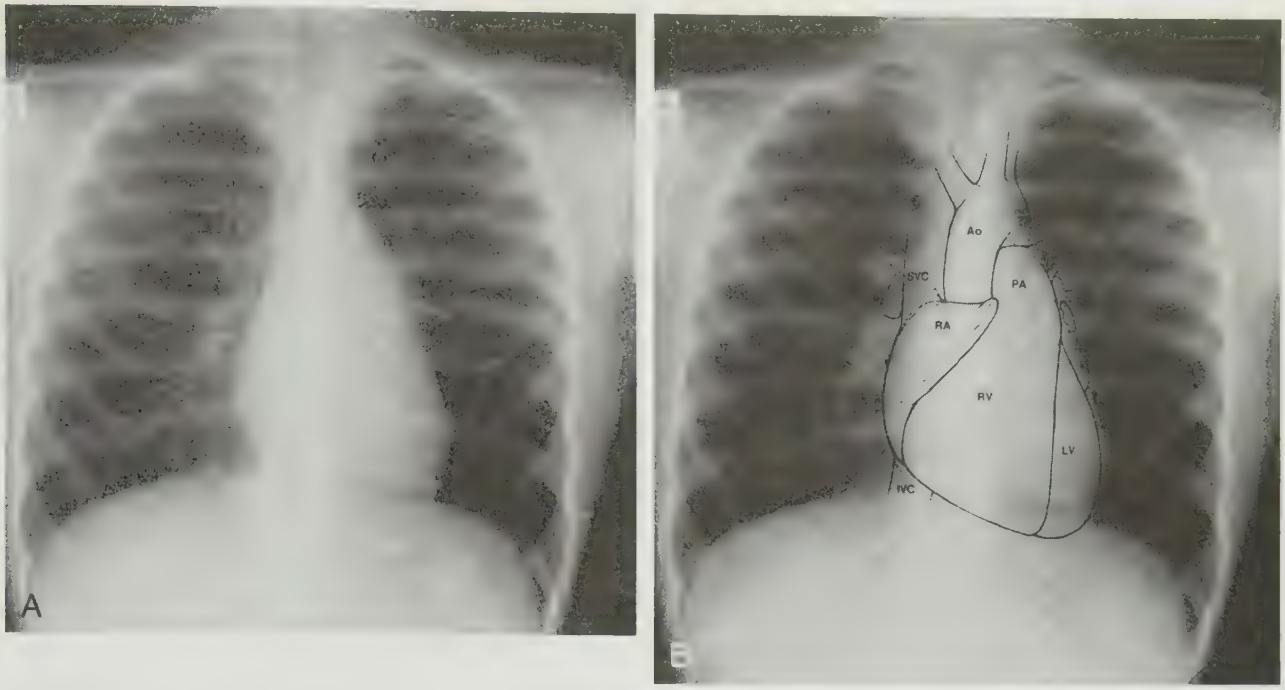

Fig. 44–1. Normal posteroanterior chest radiograph in a 10-year-old child. (A) PA view with barium in the esophagus. (B) Drawing of anatomic chambers identified in the PA view.

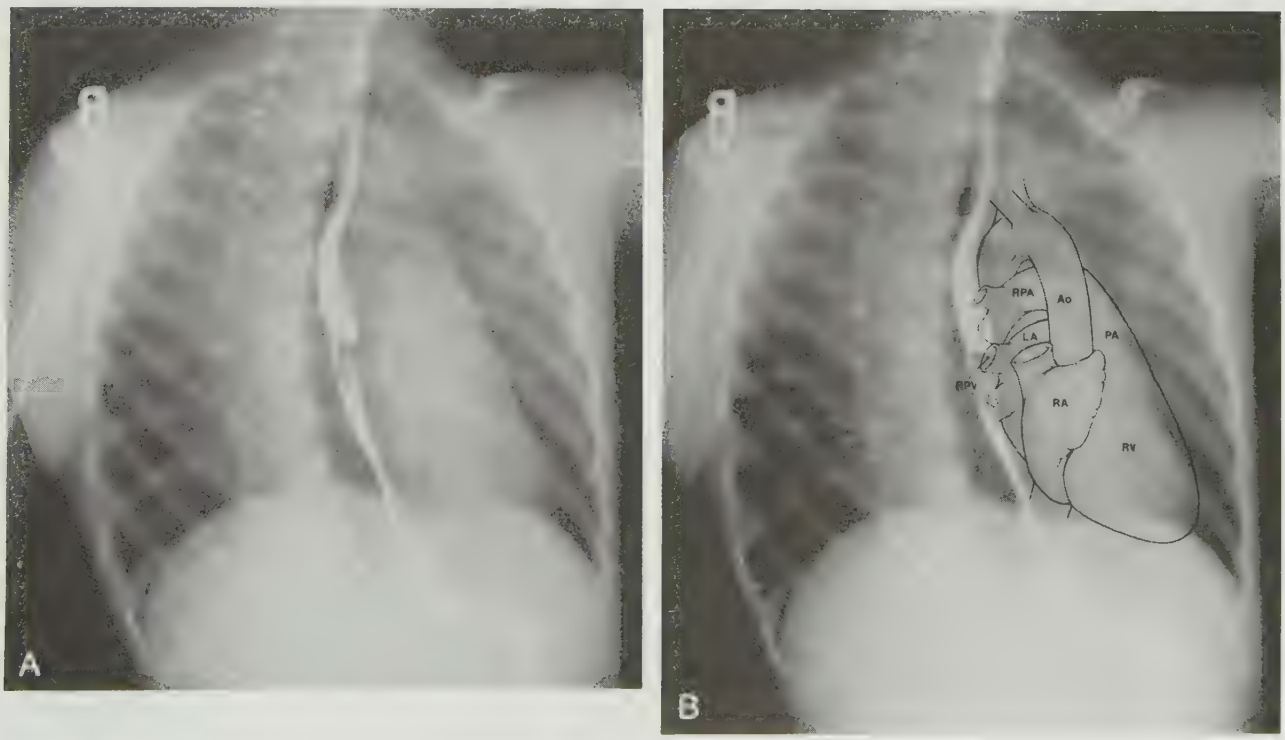

Fig. 44–2. Right anterior oblique view. (A) The concavity on the upper anterior portion of the esophagus is produced by the aortic arch. There is no posterior displacement of the left atrium. (B) Drawing of cardiac chambers in this view. Note the proximity of the left atrium to the lower third of the esophagus and the proximity of the aortic arch to the upper portion of the esophagus.

teriorly and to the right, thereby displacing the esophagus posteriorly and to the right.

In the left anterior oblique view (LAO), the left side of the chest is against the cassette with the right side approximately 60° from the flat surface of the cassette (Fig. 44–3). This position can be recognized easily because the anterior chamber that is the right ventricle does not extend to the chest wall. The posterior chamber is the left ventricle. Increased convexity, or a decrease in the distance between the anterior cardiac chamber (right ventricle) and the chest wall, suggests right ventricular dilatation. If the esophagus contains contrast media, a right aortic arch can be identified indenting the esophagus. The main advantage of this view is to evaluate right and left ventricular dilatation.

In the lateral view (Fig. 44–4), the right ventricle constitutes the lower one-half to two-thirds of the anterior cardiac border and lies behind the sternum. The upper third constitutes the right ventricular outflow tract and pulmonary artery root. The space above the origin of the pulmonary artery is occupied by the thymus; past infancy, this is a clear area of aerated lung. The upper half of the posterior cardiac border consists of the left atrium, and the lower half includes the left ventricle.

Because of the additional radiation involved in obtaining multiple views and because other modalities are available to evaluate cardiac size, the oblique views are rarely necessary and barium ingestion is now used primarily for the evaluation of a suspected vascular ring. However, posteroanterior and lateral chest radiographs are valuable in screening and are justifiably obtained as part of the initial workup of patients with suspected heart disease. All areas included on the radiograph are best observed systematically including the cervical spine, shoulder girdles, thoracic cage and chest wall, and the subdiaphragmatic areas. For example, children with Down syndrome frequently have only 11 ribs and double manubrial ossification centers. Premature fusion of sternal segments is common in many cases of cyanotic heart disease. A straight thoracic spine and decrease in the anteroposterior dimension of the chest (straight back syndrome) may be responsible for a functional murmur.[8] Pectus excavatum apparent on the lateral film may explain the AP film appearance of displacement of the heart into the left chest and exposure of the right hilar area mimicking pulmonary pathology. Kyphoscoliosis may produce marked displacement of mediastinal structures, making radiographic evaluation of the heart and lungs difficult.[9] Scoliosis is present in 6% of patients with cyanotic heart disease. A coarse and trabecular pattern with expansion of the medullary cavity of the ribs is expected in chronic anemias and cyanotic heart disease, and rib notching is an expected finding in older patients with coarctation of the aorta. Unilateral rib notching is also a common finding following a Blalock-Taussig procedure (subclavian-pulmonary artery anastomosis).[10]

The subdiaphragmatic organs such as the stomach and liver should be identified in order to recognize situs inversus. There are four major considerations regarding the recognition of abdominal viscera.[11] Situs (position) solitus (usual) is usually associated with a normal heart and normal bronchial divisions. In situs inversus, true mirror image dextrocardia is frequently present; in this condition, the aortic arch is on the right. This should not be confused

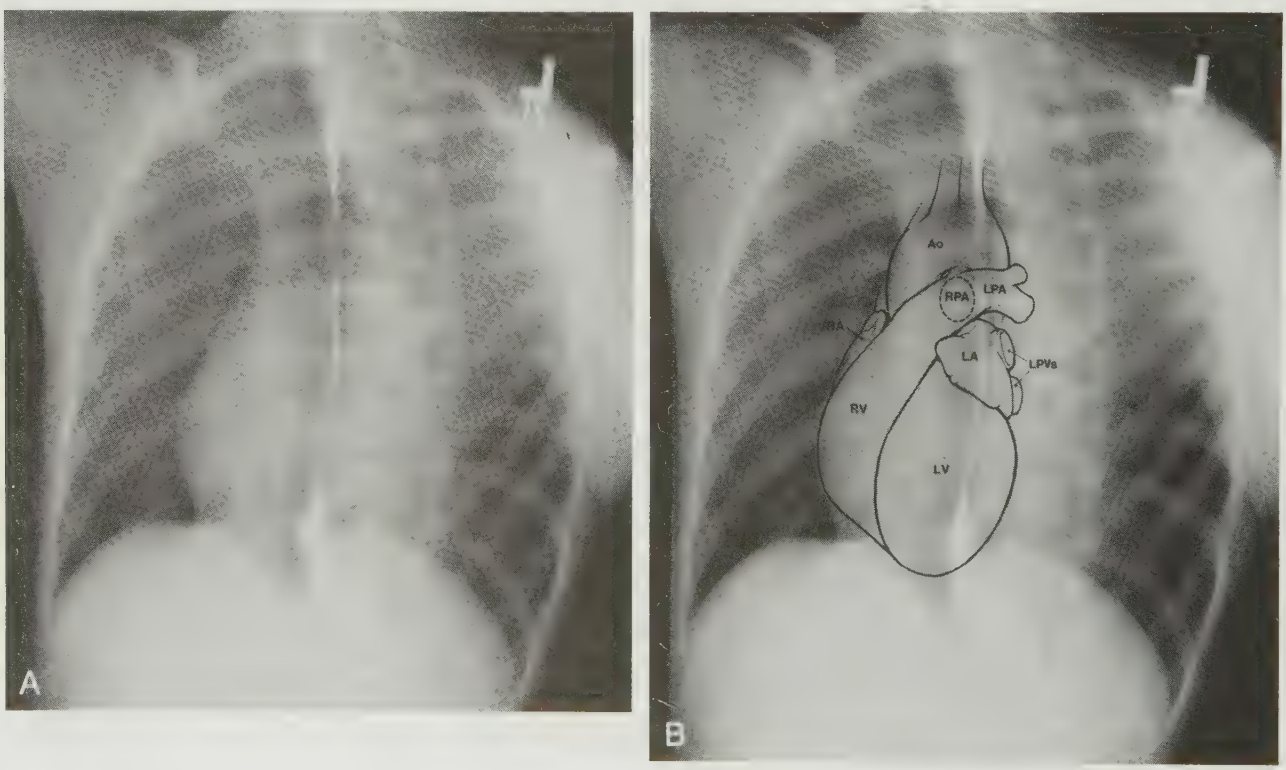

Fig. 44–3. Left anterior oblique view. (A) Note the greater distance between the anterior cardiac border (right ventricle) and the anterior chest wall compared to the right anterior oblique view (see Fig. 44–2). (B) Drawing of cardiac chambers showing most of the anterior cardiac silhouette. In this view, the right ventricle is anterior and the left ventricle is posterior.

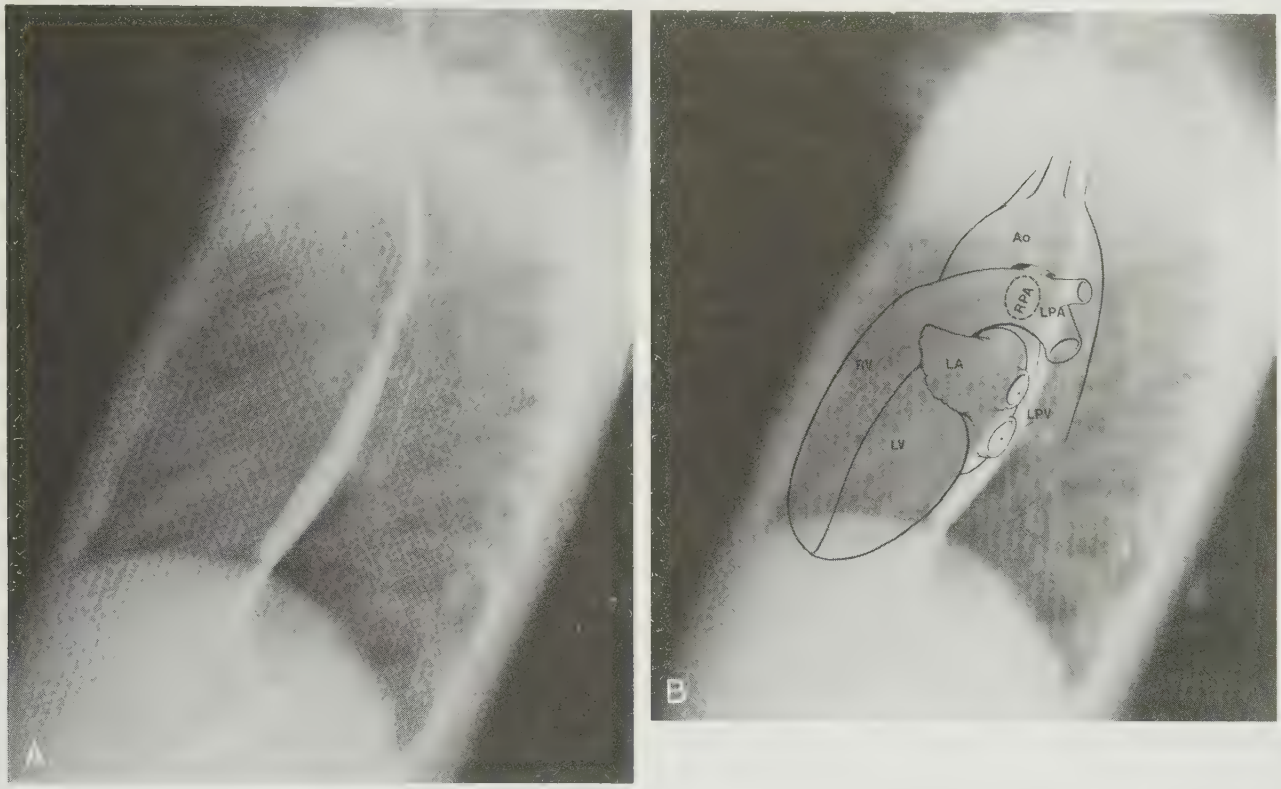

Fig. 44–4. Lateral view. (A) Radiograph shows normal configuration of the esophagus with slight indentation in the upper portion produced by the aortic arch. (B) Anatomic drawing showing the proximity of the right ventricle to the anterior chest wall.

with dextroversion, in which the aortic arch remains on the left with the configuration and position of the heart to the right of the midline of the chest similar to dextrocardia. In true situs inversus with dextrocardia, there is also inversion of the lungs.[12] In other words, the left-sided lung has three lobes and the right two. The incidence of cardiac anomalies with situs inversus may be up to twice that of situs solitus.[13] Correct labeling of the radiograph as to right and left sides is important to avoid a mistaken diagnosis of dextrocardia and situs inversus.

Thus, there are two long bronchi of equal length with a wider-than-normal midline angle. In the polysplenia syndrome, there are usually two bilobed lungs (left-sided pulmonary isomerism).[14–16] In this condition, the stomach bubble is usually in a more medial position and the liver is also in a midline location. A common feature of this syndrome is venous drainage from the abdomen through the azygous system into the right atrium (azygous continuation of the inferior vena cava). The congenital heart diseases associated with the polysplenia syndrome typically are those anomalies associated with left-to-right shunts. These include atrial and ventricular septal defects, endocardial cushion defects, double outlet right ventricle, and patent ductus arteriosus; mixed pulmonary venous return is frequent.

The asplenia syndrome (Ivemark syndrome)[17] is associated with bilateral right-sidedness. In other words, two right lungs each contain three lobes; the major bronchi are short because of the origin of a right upper lobe bronchus bilaterally. The liver is usually in the midline position. This syndrome commonly is associated with complex or severe heart disease, often cyanotic, typified by a variety of conditions including endocardial cushion defects, pulmonary atresia or stenosis, transposition of the great vessels, and double outlet right ventricle. An evaluation of the bronchial configuration as to whether there is bilateral right-sidedness or left-sidedness is determined by high 100 kilovolts radiograph utilizing a Thoraeus filter made of copper and aluminum.[18] The presence or absence of multiple spleens is easily determined by liver–spleen nuclear scans.

RADIOGRAPHY OF CONGENITAL HEART DISEASE

Newborn

Serious cardiac malformations may be present in a newborn, but clinical manifestations may not develop until several weeks later. However, one group of cardiac anomalies can be identified clinically during the first few days of life. Among the most common are complete transposition of the great vessels, hypoplastic left ventricle, and total anomalous venous return below the diaphragm. The hypoplastic left heart syndrome is the most common cause of congestive heart failure during the first few days of life; complete transposition of the great vessels is most common in the cyanotic newborn. Severe aortic stenosis, tetralogy of Fallot, and coarctation of aorta may make their presence known clinically during the newborn period, but these are less commonly detected than the other anomalies. Newborn infants with hypoplastic left ventricle usually show cardiomegaly with increased prominence of the pulmonary venous structures. The overall appearance of these infants may be similar to that of transient tachypnea of the newborn, a condition in which there is retained fetal lung fluid

with associated cardiomegaly, prominent pulmonary veins, Kerley B lines, and fluid in the interlobar fissures and pleural space. In this latter condition, the chest radiograph returns to normal after a few days, as a result of lymphatic and capillary absorption of the fluid. In the hypoplastic left heart syndrome, the changes of congestive failure increase. Total anomalous pulmonary venous return below the diaphragm should be suspected in an infant with Kerley B lines, a heart that is normal in size and configuration, and hepatomegaly. Kerley B lines are best seen above the costophrenic sulci and appear as horizontal lines of increased density.[19] They represent fluid within the interlobular septa and lymphatics and reflect an increase in pulmonary venous pressure. Cardiomegaly and congestive heart failure also may occur in acute and chronic hypoxemic conditions, intrauterine transfusion syndrome, erythroblastosis fetalis, large hemangiomas, and especially in arteriovenous malformations such as an aneurysm of the vein of Galen.

An experienced radiologist can make a diagnosis of a specific type of congenital heart disease from conventional posteroanterior and oblique views of the chest with an accuracy of approximately 70%. The probability of including the right diagnosis within a select list of differential possibilities is over 90%.

Infancy and Childhood

In the radiologic consideration of congenital heart disease, there are five primary considerations: 1) Is the heart enlarged? 2) Which chambers are dilated? 3) Are the pulmonary arterial markings increased, decreased, or normal? 4) Is the undivided portion of the pulmonary artery convex or concave? 5) Is the aortic arch large, small, or normal in size and position in the chest?

The most important of these considerations is the evaluation of the pulmonary arterial vascularity.[20,21] If the vascularity is increased, diminished, or normal, then there are entirely different groups of differential consideration that can be further defined by evaluating cardiac chamber size, size of the pulmonary artery, and size of the aortic arch.

Differentiation of the pulmonary arteries from pulmonary veins may be made with a reasonable degree of accuracy. The pulmonary veins are straight in their course and directed toward the central portion of the heart, which is the left atrium. The pulmonary arteries, on the other hand, are more tortuous, and can be seen on end, particularly in the region of the superior hilus.

One method of determining increase or decrease in the size of the pulmonary arteries is to compare an "end on" bronchus filled with air with an adjacent "end on" artery, which should be comparable in size in the middle third of the lung field. When pulmonary vessels are enlarged, the artery is larger than the bronchus.

The following classification, based on the prominence of the pulmonary arterial markings, is valuable in determining the differential diagnosis of congenital heart lesions (Table 44–1). This does not include all examples of congenital heart conditions because many forms defy description. In addition, the evaluation of congenital heart disease is not entirely a radiologic problem. Rather, it is a cooperative effort between the radiologist and the cardiologist, synthesizing the information obtained from electrocardiography, echocardiography, and cardiac catheterization.

If we can conclude that the pulmonary arterial markings are increased, we can usually assume that one of the following conditions is present: atrial septal defect, ventricular septal defect, atrioventricular canal, patent ductus arteriosus, anomalous pulmonary venous return, true truncus arteriosus, or uncomplicated transposition of the great vessels. Corrected transposition (ventricular inversion) also may be included because this is usually associated with a ventricular septal defect. In this group with increased vascular markings are further findings that are helpful in determining which further condition is present. In each of the defects in which there are increased pulmonary arterial markings, there is increased pulmonary flow. If there is associated pulmonary hypertension with increased resistance, the reliability of an evaluation based on the prominence of the arterial markings is less accurate.

Congenital cardiac defects in which there are decreased pulmonary arterial markings include tetralogy of Fallot, pseudotruncus (which is a variation of tetralogy of Fallot with pulmonary artery atresia rather than pulmonary stenosis), various types of tricuspid atresia, and Ebstein's malformation.

In a number of conditions, the pulmonary arterial markings are normal—namely, aortic stenosis, endocardial fibroelastosis, coarctation, congenital mitral stenosis, cor triatriatum, pulmonary valvular stenosis, and idiopathic dilation of the pulmonary artery. In this group, increased pulmonary venous pressure may be present with resulting increased prominence of the pulmonary venous markings and Kerley B lines. In such conditions, the accurate differentiation of pulmonary arteries from veins becomes difficult but not impossible. Also, the presence of complicating bronchopneumonia makes it more difficult to determine whether or not the arterial markings are increased, decreased, or normal. Pneumonia as a complication of congenital heart disease is much more

Table 44–1. Radiologic Considerations of Congenital Heart Disease

Increased Pulmonary Vascularity	*Decreased Pulmonary Vascularity*	*Normal Pulmonary Vascularity*
1. Atrial Septal Defect	1. Tetralogy	1. Aortic Stenosis
2. Ventricular Septal Defect	2. Pseudotruncus	2. Endocardial Fibroelastosis
3. AV Commune	3. Tricuspid Atresia	3. Coarctation
4. Ductus	4. Ebstein's Malformation	4. Congenital Mitral Stenosis
5. Partial Anomalous Venous Return	5. Pulmonary Hypertension	5. Cor Triatriatum
6. Total Anomalous Venous Return	6. Transposition with Pulmonary Stenosis	6. Pulmonary Valvular Stenosis
7. Truncus Arteriosus		7. Idiopathic Dilatation of the Pulmonary Artery
8. Transposition		
9. Corrected Transposition		

common in association with a left-to-right shunt, because of compression of the dilated pulmonary arteries on the bronchial tree with resultant obstruction. In addition, air trapping of a lobe or pulmonary segment can occur and simulate congenital lobar emphysema.[22] The common sites of compression are the left main stem bronchus and the left upper and right middle lobe bronchus.

Increased Pulmonary Arterial Markings

Atrial Septal Defect

The usual atrial septal defect of the secundum type shows radiographic evidence of increased arterial markings, slight or moderate enlargement of the heart, convexity of the undivided pulmonary artery segment with a small aorta, and no evidence of left atrial enlargement as determined by absence of esophageal displacement in the right anterior oblique view (Fig. 44–5). Partial anomalous pulmonary venous return produces an identical radiographic appearance. One type of anomalous pulmonary venous return occurs in the "scimitar sign," in which a single large pulmonary vein (usually on the right) empties into the right atrium or inferior vena cava (Fig. 44–6). Atrial septal defect of the secundum type does not typically show left atrial enlargement due to the ease with which the atrium can "decompress" in the presence of a large atrial communication. One exception is that some of the ostium primum defects will show left atrial enlargement, particularly when mitral insufficiency (common in this anomaly due to cleft mitral valve) is present. If there is no left atrial enlargement, if there is the combination of a small aortic knob, a prominent pulmonary artery segment, and increased pulmonary vascularity, the lesion is probably an atrial septal defect or partial anomalous pulmonary venous return.

Ventricular Septal Defects

There are several different anatomic locations for ventricular septal defects with radiologic expression reflecting the size and direction of the shunt. Normal radiographs commonly are present with small defects (Fig. 44–7). Pulmonary vascular markings begin to appear prominent when pulmonary to systemic flow ratios (Q_p/Q_s) are 1.7/1 or more. The pulmonary vascular markings are increased, the aortic knob is small, the pulmonary artery segment convex, and there is usually evidence of left atrial enlargement in the right anterior oblique projection (Fig. 44–8). Most of the ventricular septal defects with a significant left-to-right shunt will show left atrial enlargement. Restrictive ventricular septal defects with a small left-to-right shunt and a pulmonary artery pressure less than 50% of the systemic pressure frequently show no radiographic abnormality. Ventricular septal defects with significant pulmonary hypertension (pulmonary artery pressure 85% of or equal to the systemic pressure) and with a balanced or reversed shunt (right to left across the defect) show little or no cardiac enlargement. These defects also have decreased peripheral arterial markings, an increase in size of the right and left pulmonary arteries at the hilus, and less evidence of left atrial enlargement (Fig. 44–9).[22] Recurrent pneumonia and segmental areas of air trapping are common in large left-to-right shunts (Fig. 44–10). The segments of air trapping should not be confused with congenital lobar emphysema.

Atrioventricular Canal

The radiographic features of atrioventricular canal defects are similar to ventricular septal defects except the heart is usually larger in the canal defect. This is particularly true in young infants in whom the heart may be markedly dilated and is also more globular or rounded than it is in isolated ventricular septal defect (Fig. 44–11). This is the most common cardiac lesion associated with Down syndrome.

Patent Ductus Arteriosus

The radiographic features of patent ductus arteriosus resemble those of ventricular septal defects except for a larger aortic arch. This difference is impossible to evaluate in the infant, but in the older child or adult it is usually apparent. In older children and adults, pulmonary arterial markings are increased; the undivided portion of the pulmonary artery is prominent and the left atrium is usually dilated.

The younger the patient, the more difficult is the evaluation of radiographic findings. But with increasing age, these differentiating features become more characteristic (Fig. 44–12).

Total Anomalous Venous Return (TAPVR), Supracardiac

This represents one type of congenital heart disease in which the radiographic findings may be pathognomonic (Fig. 44–13). In the most common type, pulmonary veins drain into a common chamber that empties by way of a left vertical vein into the innominate vein, to the right superior vena cava, and into the right atrium. In such cases, there is characteristic widening of the superior mediastinum that produces a "snowman" or "figure-eight" silhouette. Distention of the right superior vena cava and left vertical vein accounts for the "snowman" configuration. The heart is enlarged with convexity of the pulmonary artery segment and increased pulmonary arterial markings.

Total Anomalous Venous Return (TAPVR) Below the Diaphragm

The heart in this condition is usually of normal size (Fig. 44–14). Pulmonary vascular markings are poorly defined, and the overall appearance is more suggestive of passive venous congestion, bronchopneumonia, or hyaline membrane disease. The heart is not dilated because of the obstruction to venous return within the liver. The radiographic identification of Kerley B lines, normal heart size, and configuration with clinical evidence of hepatomegaly strongly suggests TAPVR below the diaphragm. Other differential considerations include pulmonary vein atresia or stenosis, cor triatriatum, and congenital mitral stenosis.

In transient tachypnea of the newborn (wet lung syndrome), which results from retained fetal lung fluid, Kerley B lines may be prominent, but the cardiac enlargement and pleural effusion differentiate this condition from total anomalous venous return below the diaphragm. Severe pulmonary lymphangiectasis in the newborn may resemble TAPVR below the diaphragm, but the clinical findings, catheterization data, and angiocardiography are differentiating procedures. Pulmonary arteriograms in a patient with intradiaphragmatic TAPVR demonstrate the return of pulmonary venous blood into a common venous trunk which passes through the diaphragm into the portal vein or inferior vena cava.

True Truncus Arteriosus

The pulmonary arterial markings in patients with true truncus arteriosus are usually greatly increased (Fig. 44–15). In addition, the heart is enlarged and the pulmonary artery segment is concave.

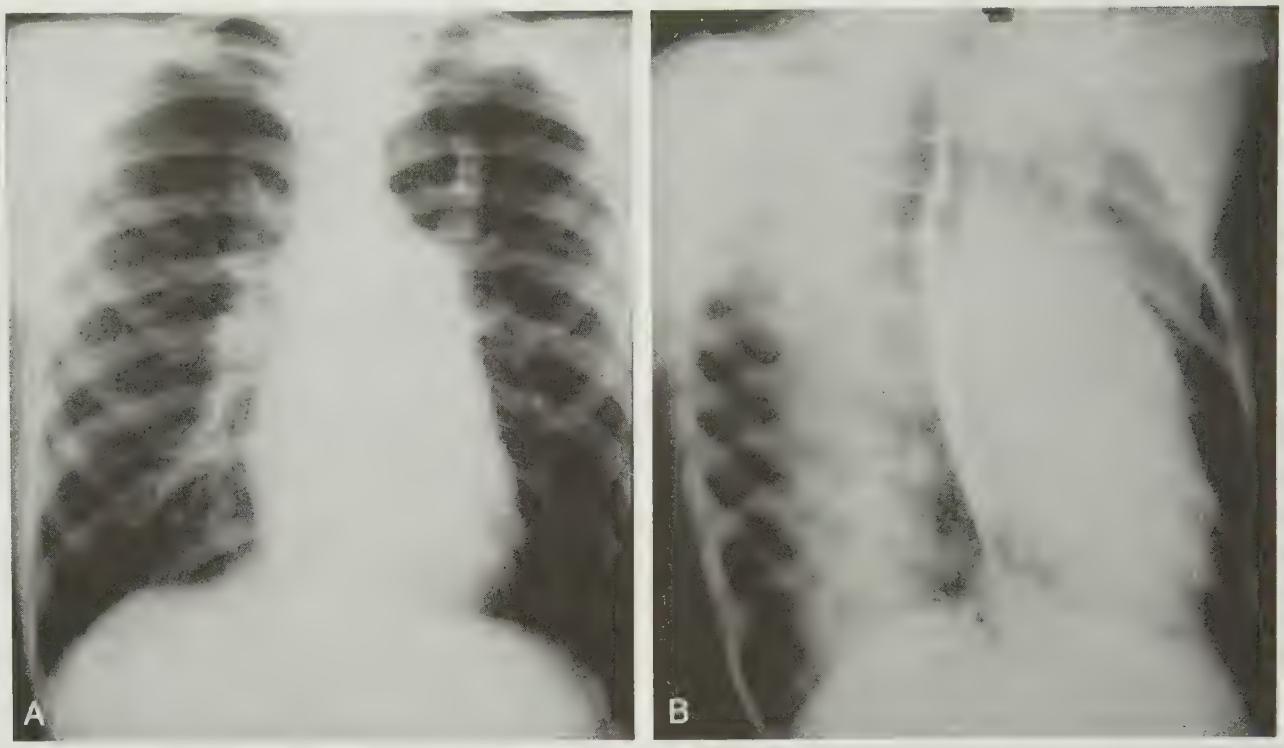

Fig. 44–5. Atrial septal defect (secundum type). (A) Posteroanterior chest radiograph shows a normal-sized heart but increased pulmonary arterial markings. The main pulmonary artery segment is convex and the aortic arch is normal (or perhaps slightly small). (B) Right anterior oblique view shows no evidence of left atrial displacement of the esophagus.

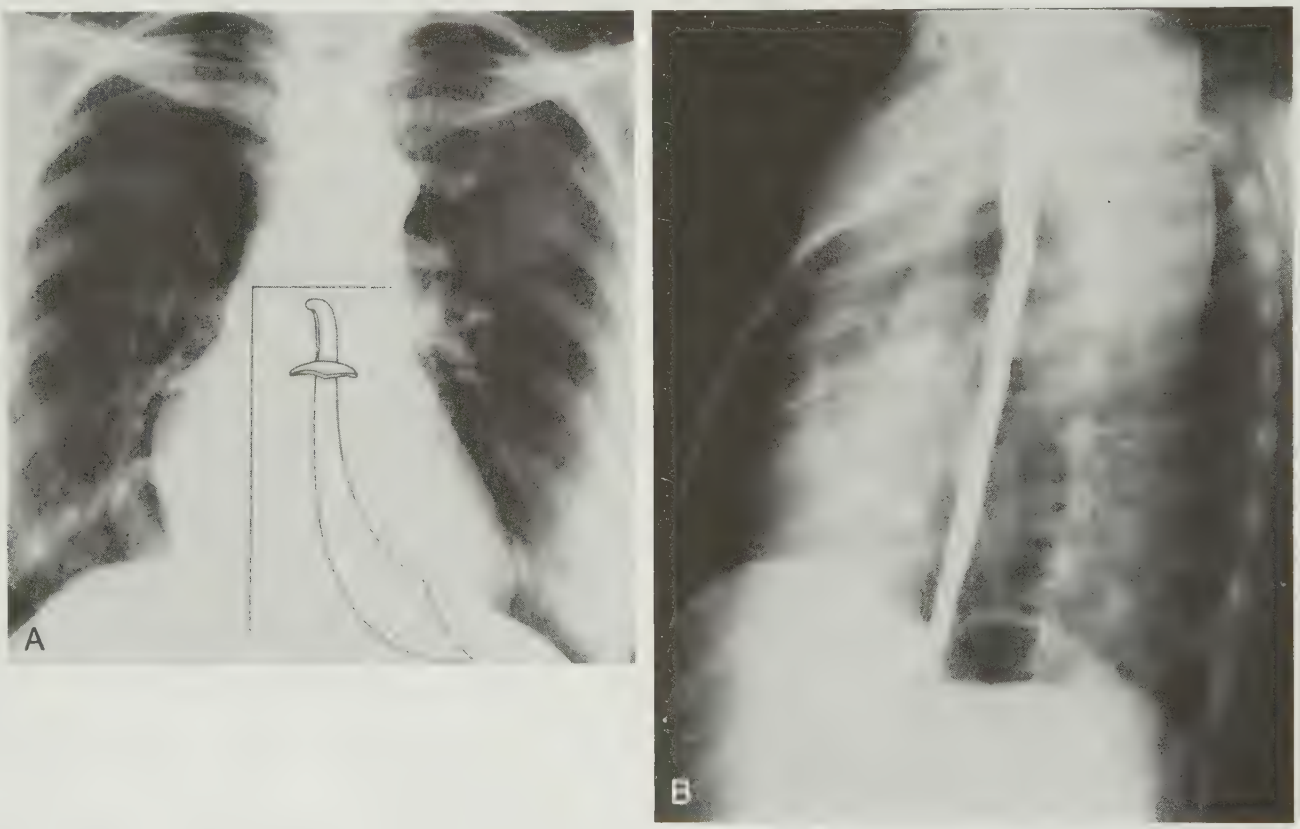

Fig. 44–6. Anomalous pulmonary venous return (scimitar sign). (A) An anomalous vein is adjacent to and parallels the right atrium. (B) Left anterior oblique view shows the anomalous vein terminating in a round area of increased density identifying its entrance to the right atrium.

Fig. 44–7. Small ventricular septal defect. The chest radiograph is normal.

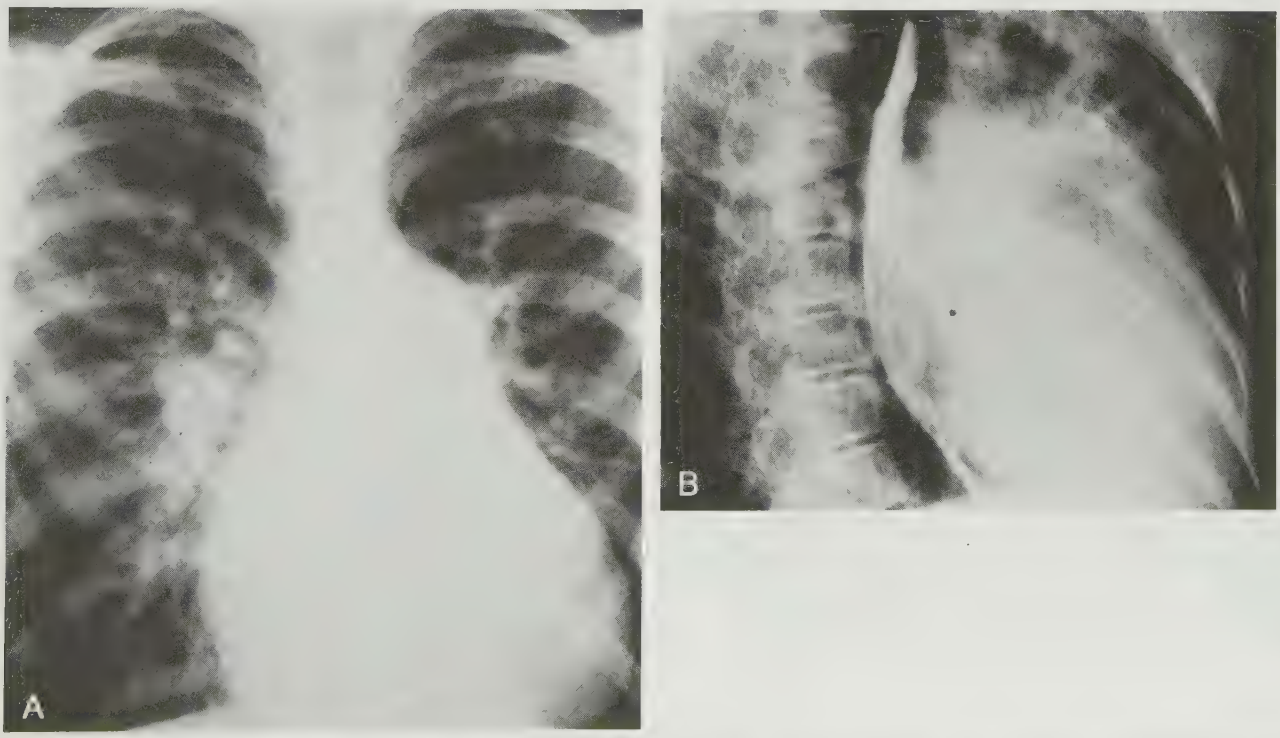

Fig. 44–8. Ventricular septal defect with large left-to-right shunt. (A) The heart is enlarged, pulmonary arterial markings are increased, the undivided portion of the pulmonary artery is abnormally convex, and the aortic arch is small. (B) Right anterior oblique view shows displacement of the esophagus by the dilated left atrium. There is minimal impression of the small aortic arch on the upper portion of the esophagus.

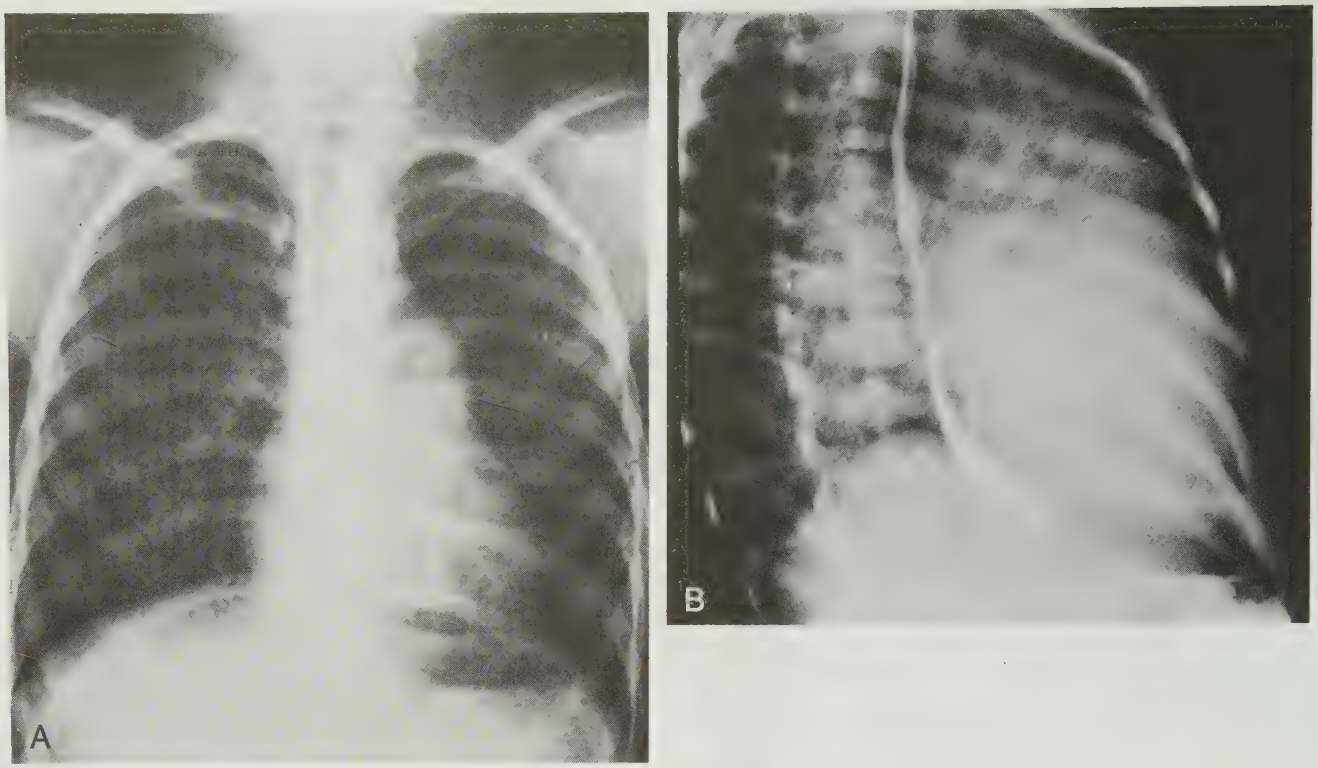

Fig. 44–9. Ventricular septal defect with pulmonary hypertension and right-to-left shunting. (A) The heart is of normal size, the main pulmonary artery is convex, the aortic arch is small, and pulmonary peripheral vessels are diminished. (B) Right anterior oblique view shows minimal posterior displacement of the esophagus by the left atrium.

Fig. 44–10. Ventricular septal defect. The heart is slightly enlarged, and pulmonary arteries are markedly increased. Perihilar pneumonia is present and the right middle lobe shows increased aeration due to air trapping.

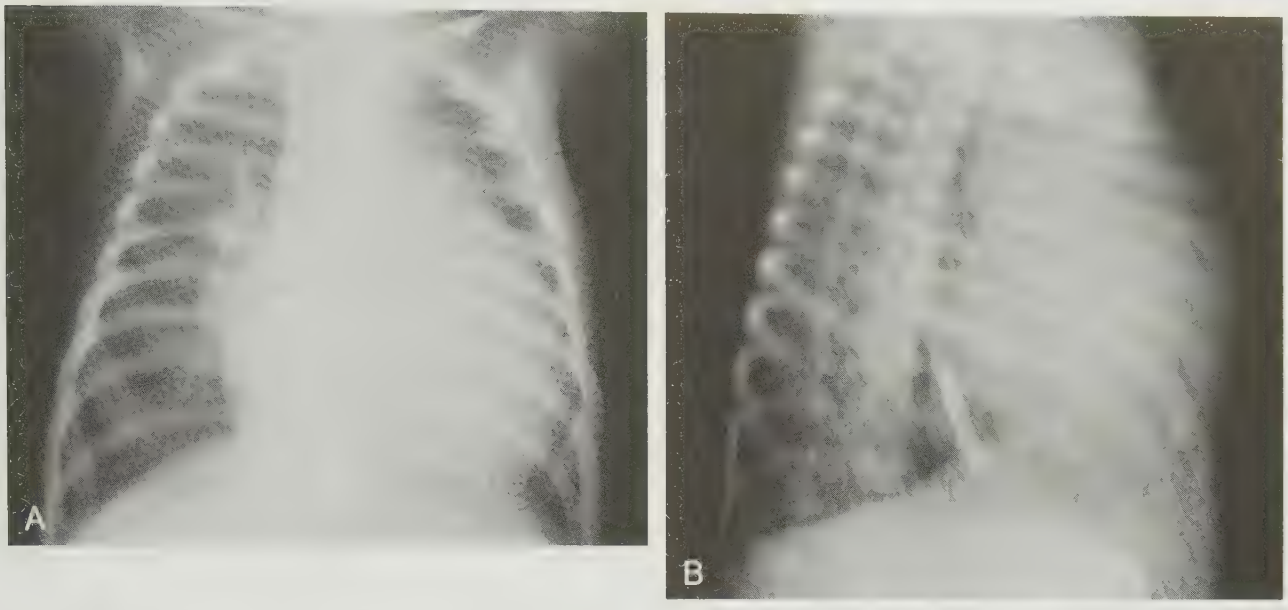

Fig. 44–11. Atrioventricularis communis. (A) The heart is enlarged and has a globular configuration. The pulmonary arterial markings are increased and the esophagus is displaced slightly to the right by the dilated left atrium. (B) Right anterior oblique view shows that all chambers are dilated with posterior displacement of the esophagus by the left atrium.

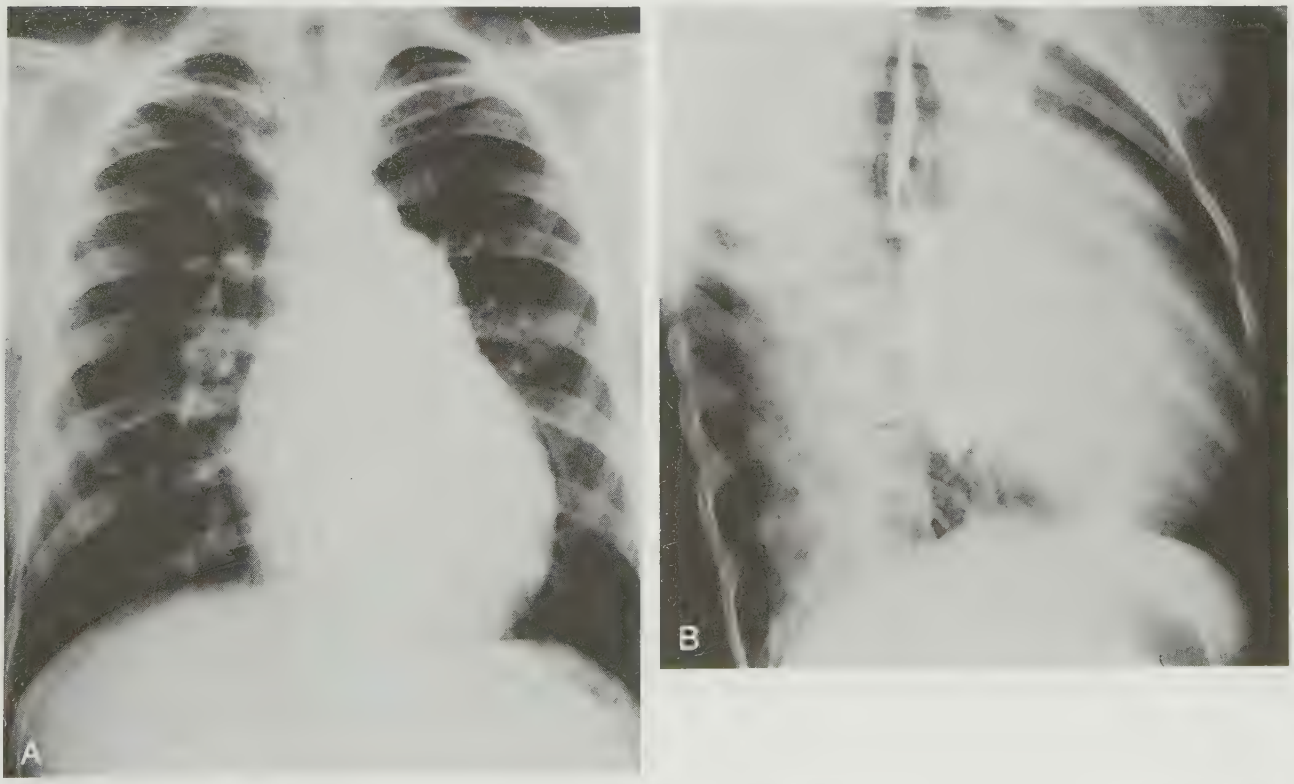

Fig. 44–12. Patent ductus arteriosus. (A) The heart is slightly enlarged, the main pulmonary artery is convex, and the aortic arch immediately above this is abnormally prominent. (B) Right anterior oblique view shows displacement of the esophagus by the dilated left atrium. Above this, the esophagus is significantly indented by the large aortic arch.

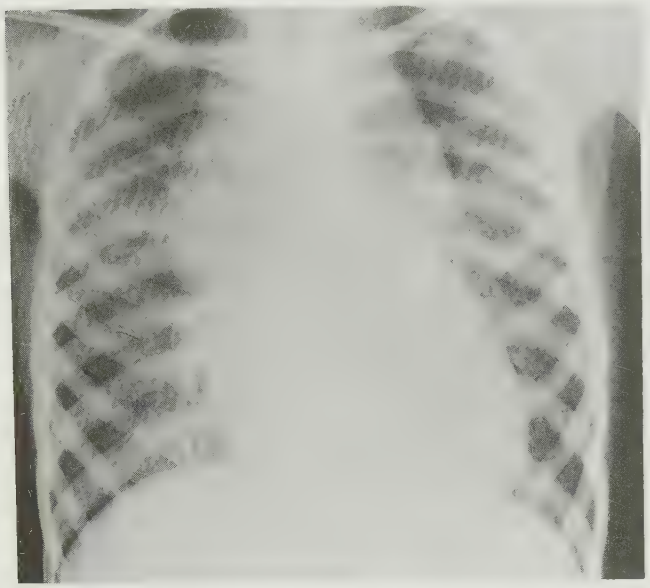

Fig. 44–13. Total anomalous venous return above the diaphragm. The heart is enlarged, pulmonary arterial markings are increased, and there is dilatation of the right and left superior venae cavae, resulting in the wide superior mediastinum.

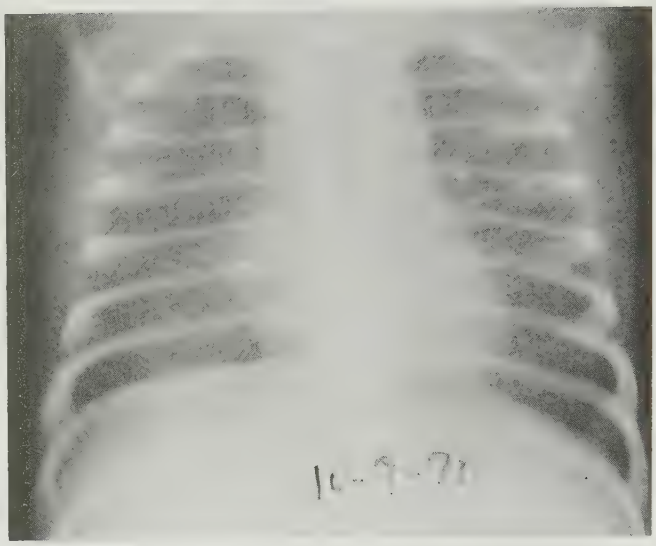

Fig. 44–14. Total anomalous venous return below the diaphragm in a newborn infant. The heart is of normal size. Pulmonary venous pattern is increased and ill-defined Kerley B lines are seen above the costophrenic sulci. On physical examination, the liver was enlarged.

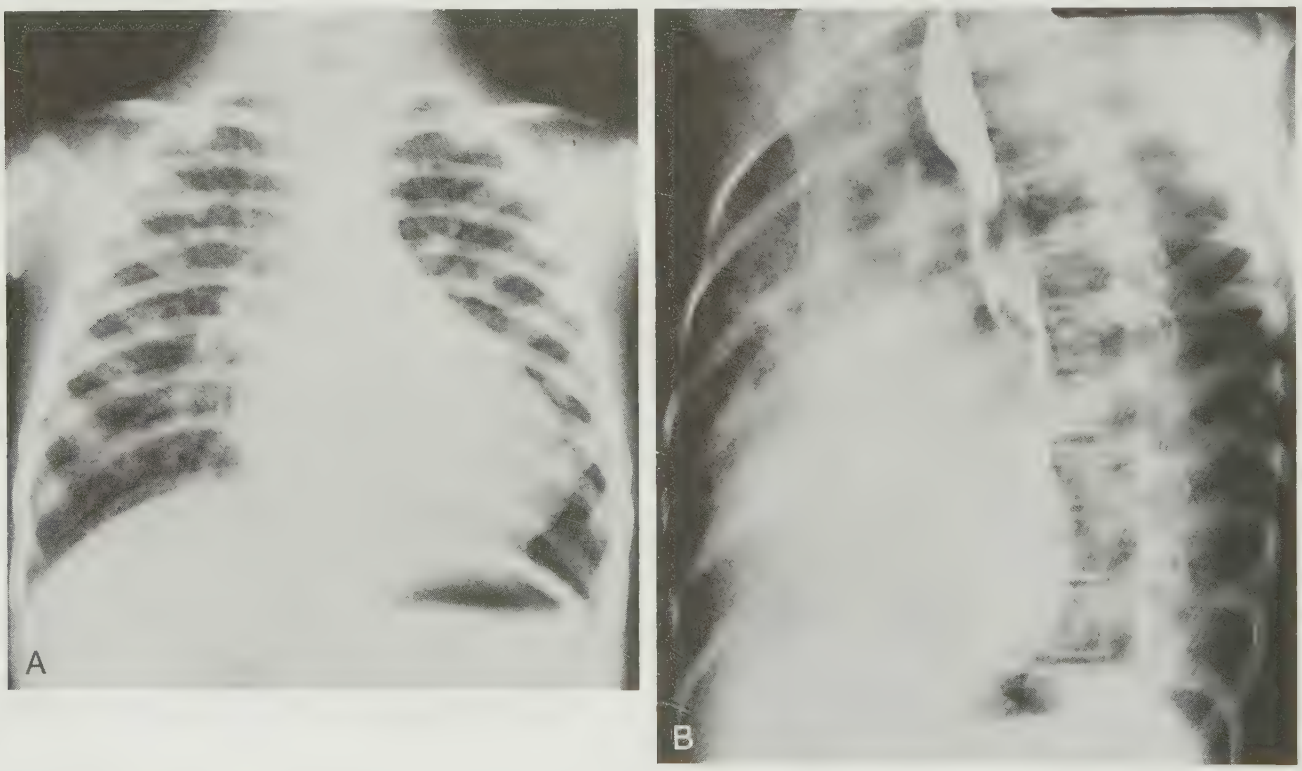

Fig. 44–15. True truncus arteriosus (Type I). (A) The heart is enlarged and pulmonary arterial markings are increased in prominence. The superior mediastinum is narrow. (B) Left anterior oblique view shows the enlargement of both right and left ventricles. Note the indentation on the anterior portion of the upper esophagus produced by a right aortic arch.

Both ventricles are prominent, and there is evidence of left atrial dilatation. A right aortic arch occurs in approximately 25% of patients with truncus arteriosus and, consequently, the combination of cardiac enlargement, increased pulmonary vascularity, and a right aortic arch, is very suggestive of this condition.

In complete transposition, the aorta arises from the right ventricle and is usually anterior to the pulmonary artery, which arises from the left ventricle. Obviously, various intra- and extracardiac communications must be present in order to sustain life.

The radiographic findings consist of cardiomegaly, increase in the pulmonary arterial markings, and a narrow superior mediastinum because of the transposed vessels (Fig. 44–16A). In the left anterior oblique view, the mediastinum may appear widened because of the transposed vessels (Fig. 44–16B). The heart frequently has an oval or egg-shaped configuration and the radiographic features may be otherwise very similar to true truncus arteriosus.

In corrected transposition of the great vessels, the great vessels are transposed, but the ventricles are also inverted with the aorta arising anteriorly from the inverted right ventricle and the pulmonary artery arising posteriorly from the inverted left ventricle. If a ventricular septal defect is present, the pulmonary arterial markings may be increased; but if a shunt is not present, pulmonary arterial markings will be normal and the heart will be of normal size.

In corrected transposition, the ascending aorta consequently is continuous with the left ventricle and produces a straight left cardiac border. Absence of the ascending aorta in its normal right mediastinal position results in a prominent right pulmonary artery that is in a seemingly higher location (Fig. 44–17).

Decreased Pulmonary Arterial Markings

Tetralogy of Fallot

The cardiac size and configuration of an infant with tetralogy of Fallot is frequently normal (Fig. 44–18). The so-called boot-shaped heart (from cor en sabot, which means wooden shoe) associated with tetralogy of Fallot results from right ventricular hypertrophy with the apex of the heart "upturned" and lifted off the diaphragm. This is seen in the older child or young adult. In the infant, the heart is usually normal in size but pulmonary vascular markings are diminished. However, if there is pulmonary atresia (pseudotruncus) rather than pulmonary stenosis, the apex may become elevated and a cor en sabot configuration may develop even in infants (Fig. 44–19). In both tetralogy of Fallot and pseudotruncus, the aortic arch is abnormally large, and is right-sided in approximately 25% of the patients (Fig. 44–20). The evaluation of ventricular hypertrophy is, as in the other conditions, more accurately determined by electrocardiogram or echocardiogram. Absence of the pulmonary valve with ventricular septal defect is characterized by an unusually large pulmonary artery with diminished peripheral vessels (Fig. 44–21).

Ebstein's Malformation of the Tricuspid Valve

In this condition, the posterior and septal leaflets of the tricuspid valve are abnormally displaced toward the right ventricular apex with resulting tricuspid reorganization. An atrial septal defect is commonly associated with Ebstein's malformation. The most striking radiographic findings in this condition are the large right atrium and the decreased pulmonary arterial markings (Fig. 44–22). The heart is usually enlarged, often massively, with most of the enlargement being due to the dilated right atrium.

A number of other conditions are associated with decreased pulmonary markings; most represent various forms of pulmonary stenosis with associated defects allowing right-to-left intracardiac shunting.

Normal Pulmonary Arterial Markings

In a number of congenital heart defects, the pulmonary markings are normal. Occasionally, this may be difficult to determine, not only because of the variability in prominence of arterial markings but also due to the association of congestive failure. Usually, distended veins are distinguishable as the result of their straight course toward the left atrium. Only with experience can a radiologist confidently discern these vascular differences.

Aortic Stenosis, Coarctation, and Endocardial Fibroelastosis

Infants with aortic stenosis usually show cardiac enlargement. The left atrium is dilated and may be very large displacing the esophagus to the right and posteriorly (Fig. 44–23). The pulmonary arterial markings are normal, but there may be distended veins secondary to passive venous congestion.

The radiographic findings are similar (often identical) in infants with coarctation of the aorta, endocardial fibroelastosis, and anomalous origin of the left coronary artery from the pulmonary artery. In each case, the left ventricle and left atrium are dilated and the pulmonary arterial markings are within normal limits of prominence (Fig. 44–24). With progressive dilation of the left ventricle and left atrium, compression of the left bronchus may produce air trapping with hyperinflation of the left upper lobe (Fig. 44–25) and later obstruction with resultant atelectasis of the left lung.

In older children with coarctation of aorta, the radiographic findings are similar to those found in the adult (Fig. 44–26). The heart may or may not be enlarged, the left atrium is usually not enlarged, and the arterial markings are normal. The esophageal displacement anteriorly and to the right, as the result of poststenotic dilation of the aorta below the coarcted segment, is particularly well displayed with a barium esophagram. The normal tapering of the aorta occurs at the aortic isthmus between the origin of the left subclavian artery and the ductus arteriosus or ligamentum. Immediately below the isthmus, the proximal descending aorta is frequently dilated (Fig. 44–27); this is the location of entry of the ductus arteriosus in fetal life. These normal variants may persist in infants and should not be confused with coarctation of the aorta. Rib notching is unusual before midchildhood but it is virtually pathognomonic of coarctation. Frequently, the silhouette of the aortic arch, the site of the coarctation, and the intra-aortic dilation produce a "figure-three" configuration. Further collateralization may be apparent on the lateral radiograph when viewing a tortuous soft tissue density lying parallel and adjacent to the posterior border of the sternum; this occurs because of the large collateral internal mammary arteries.

Congenital Mitral Atresia and Cor Triatriatum

Infants with either of these conditions usually have evident posterior displacement of the esophagus in the region of the left atrium. The left ventricle is not enlarged as is more accurately determined by the electrocardiogram. Pulmonary arterial markings

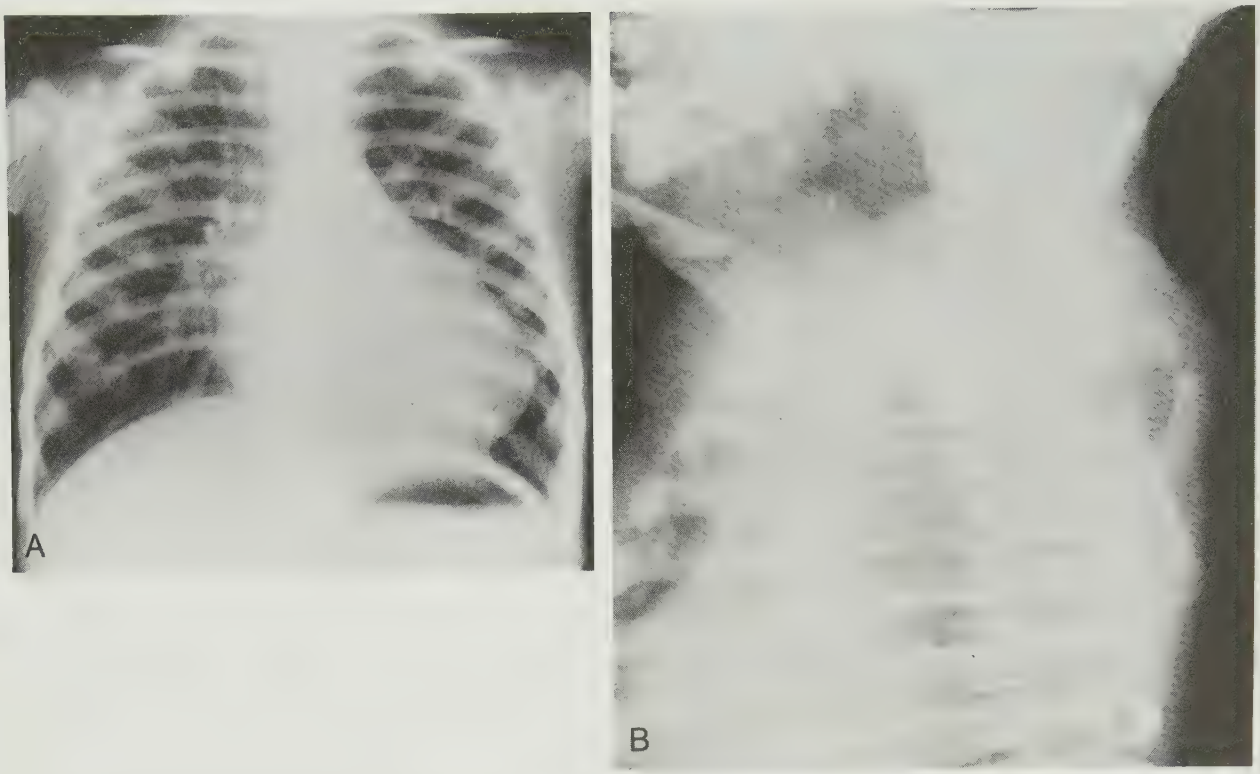

Fig. 44–16. Transposition of the great vessels. (A) The heart is enlarged and has an "egg" configuration. Pulmonary arterial markings are increased, and the superior mediastinum is narrow. (B) Left anterior oblique view shows widening of the structures in the superior mediastinum due to the anteroposterior alignment of the aorta and pulmonary artery.

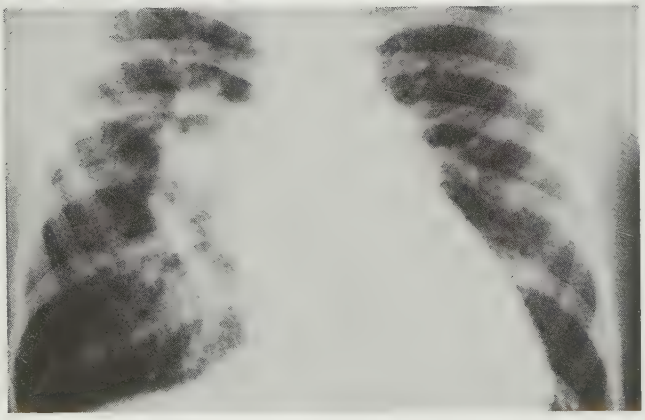

Fig. 44–17. Corrected transposition. The heart is enlarged, and pulmonary arterial markings are increased as a result of associated ventricular septal defect. The right pulmonary artery appears unusually prominent and in a high position because of the absence of the shadow of the ascending aorta usually seen in this position.

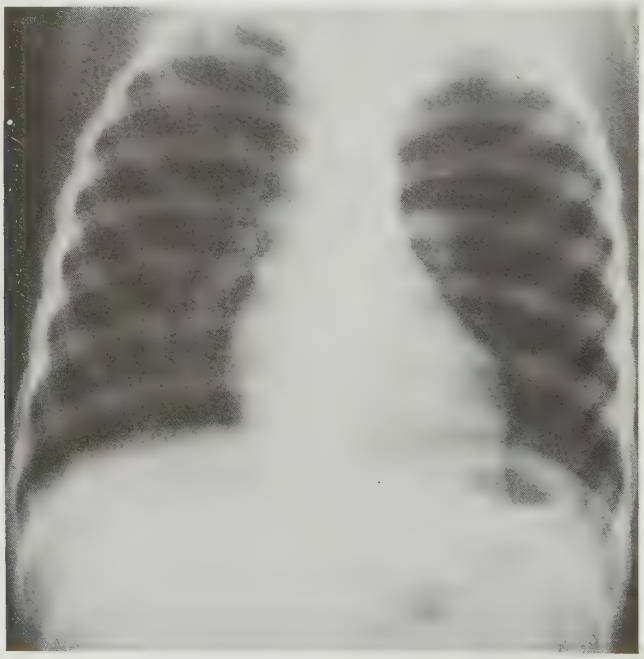

Fig. 44–18. Tetralogy of Fallot in an infant. The heart is of normal size. Aortic arch is prominent for an infant of this age, and pulmonary vascular markings are diminished.

Fig. 44–19. Pseudotruncus. Overall heart size is within normal limits. But the cardiac apex is elevated, pulmonary arterial markings are diminished, and the aortic arch is on the right.

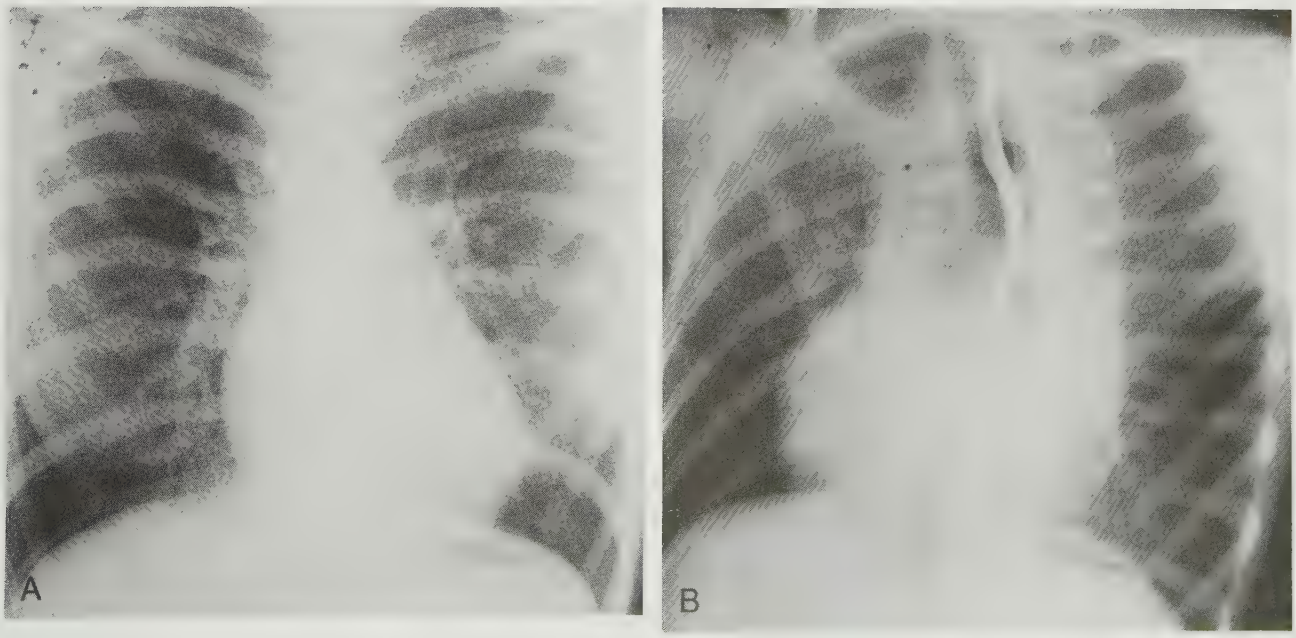

Fig. 44–20. Tetralogy of Fallot. (A) The heart is of normal size and pulmonary arterial markings are diminished. The aortic arch is on the right, displacing the esophagus to the left. (B) Left anterior oblique view showing increased convexity of the anterior chamber (right ventricle). The prominent right aortic arch displaces the esophagus posteriorly.

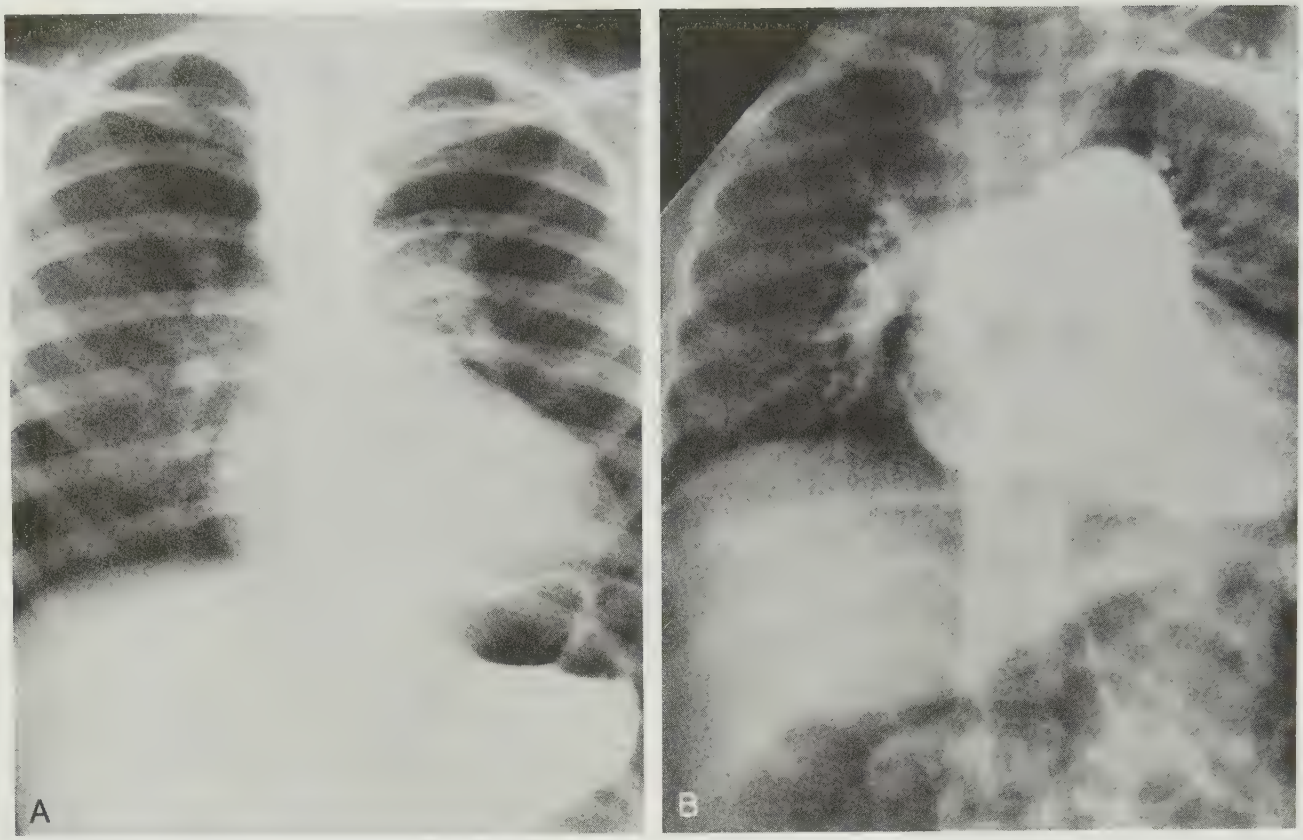

Fig. 44–21. Absence of pulmonary valve. (A) The heart size is normal, and the right and left pulmonary arteries are unusually prominent. But the peripheral vessels are diminished. (B) Angiocardiogram showing the large main pulmonary artery and right and left branches.

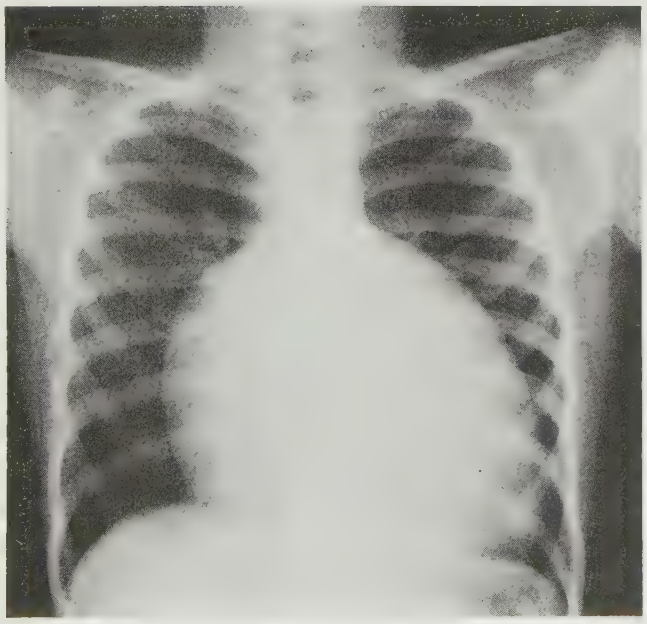

Fig. 44–22. Ebstein's malformation. The heart is enlarged with marked dilation of the right atrium and diminished pulmonary arterial markings.

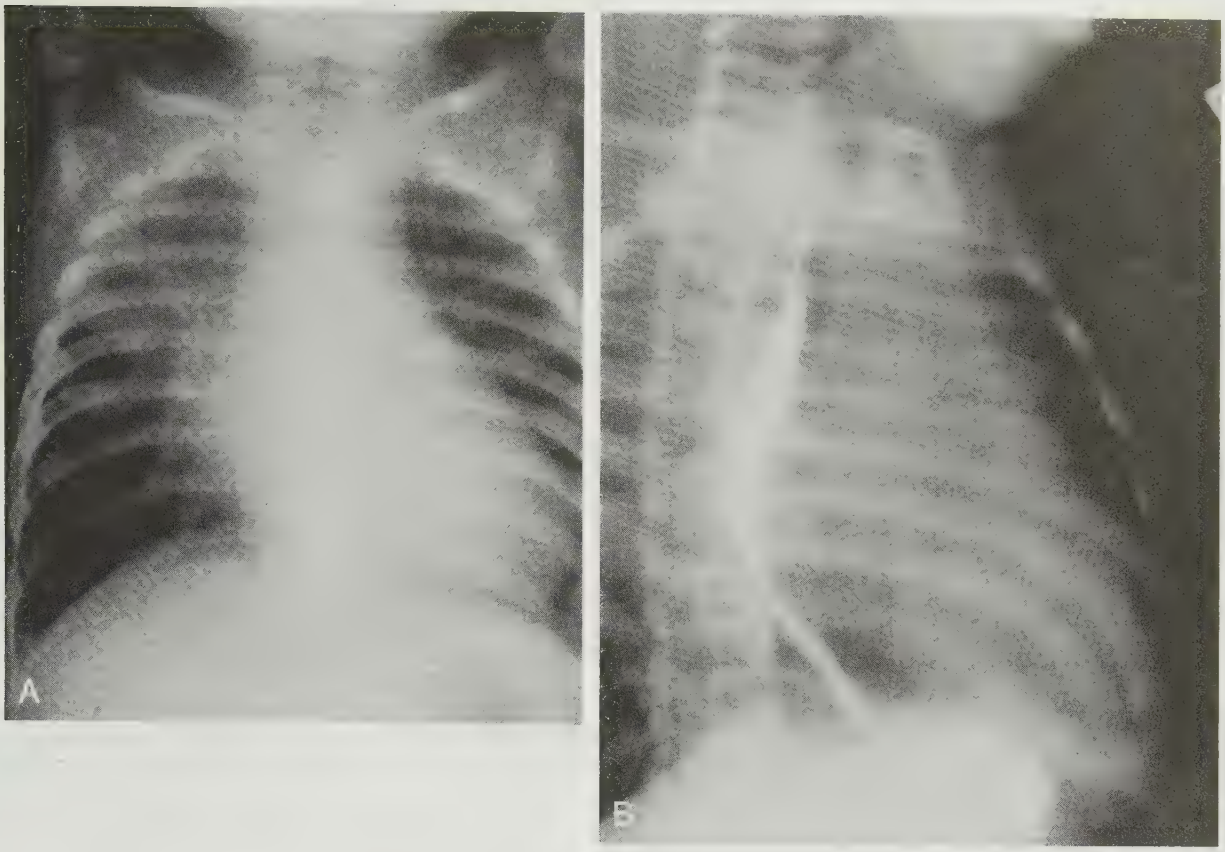

Fig. 44–23. Aortic stenosis in an infant. (A) The heart is enlarged and the left atrium displaces the esophagus to the right. Pulmonary arterial markings are normal. (B) Right anterior oblique view shows selective enlargement of the left atrium displacing the esophagus posteriorly.

are not increased, but there is evidence of passive venous congestion (Fig. 44–28).

Pulmonary Valvular Stenosis

Isolated pulmonary valvular stenosis with an intact ventricular septum usually is associated with normal pulmonary markings. Occasionally, the markings may be diminished if there is an associated atrial septal defect allowing a right-to-left shunt. The heart is normal in size or enlarged, and the pulmonary artery segment is often convex due to poststenotic dilation (Fig. 44–29). The dilated pulmonary artery is the most striking radiographic feature.

Idiopathic Dilation of the Pulmonary Artery

In this condition, the pulmonary artery is abnormally prominent resembling pulmonary valvular stenosis; but pressure studies are normal and the patients are asymptomatic. There is usually a short murmur attributed to ejection of blood into the dilated pulmonary artery, preceded by an ejection sound. The electrocardiogram should be normal with no evidence of right ventricular hypertrophy. Radiographic distinction between idiopathic dilation of the pulmonary artery and small atrial septal defect or pulmonary valve stenosis may not be possible.

Vascular Ring

There are a variety of vascular rings, most of which are responsible for inspiratory and expiratory stridor as well as more severe forms of respiratory distress. Chronic or recurrent pneumonia, particularly on the right, is commonly associated with ring anomalies. The most common vascular anomalies that encircle the trachea and esophagus are a double aortic arch (with a common descending aorta usually on the left) and a right aortic arch (with a ligamentum arteriosum or ductus arteriosus). A double arch is the type of ring most likely to cause symptoms in early infancy. In a double aortic arch as well as in a right arch with a ligamentum arteriosum or ductus arteriosus, radiographs of the esophagus show compression on the anterior portion of the trachea and on the posterior portion of the esophagus.

A retroesophageal subclavian artery is usually an incidental finding identified by an oblique defect on the posterior portion of the esophagus extending obliquely upward from left to right.

Left pulmonary artery sling anomaly is another vascular defect that may be responsible for respiratory disturbance or recurrent pneumonia. In this condition, the left pulmonary artery passes behind the trachea and in front of the esophagus. In so doing, it compresses the posterior tracheal wall or left main-stem bronchus and the adjacent anterior wall of the esophagus. These vascular anomalies are discussed in greater detail in Chapter 82.

Postoperative Radiographs

Immediately following surgical correction of the cardiac abnormality, a chest radiograph should be obtained to determine the degree of pulmonary expansion and cardiac size; the presence or

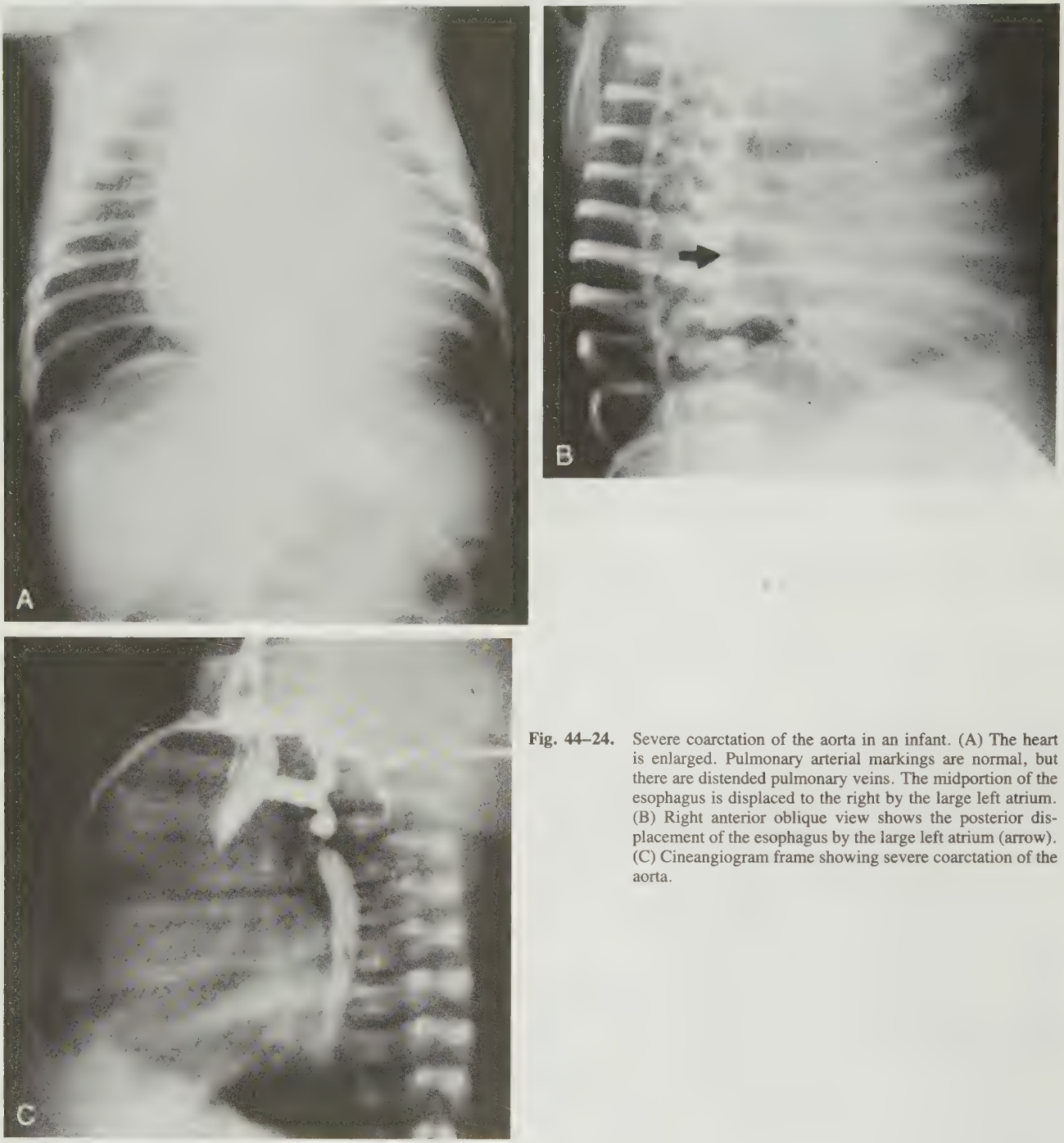

Fig. 44–24. Severe coarctation of the aorta in an infant. (A) The heart is enlarged. Pulmonary arterial markings are normal, but there are distended pulmonary veins. The midportion of the esophagus is displaced to the right by the large left atrium. (B) Right anterior oblique view shows the posterior displacement of the esophagus by the large left atrium (arrow). (C) Cineangiogram frame showing severe coarctation of the aorta.

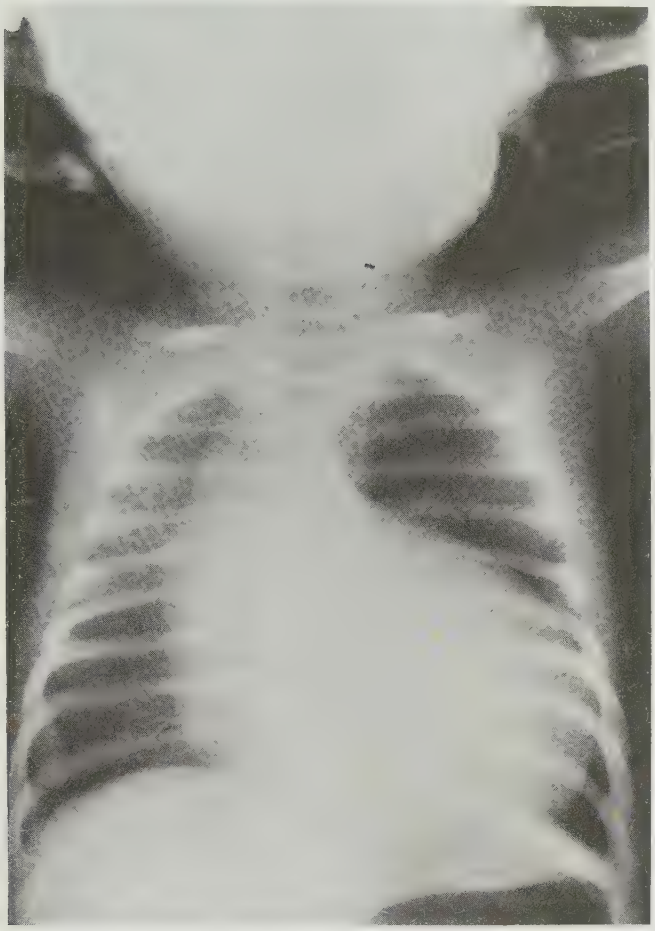

Fig. 44–25. Endocardial fibrosis in an infant. The heart is dilated and pulmonary arterial markings are within normal limits. The left upper lobe shows increased radiolucency due to air trapping.

Fig. 44–26. Coarctation of the aorta in an older child. Chest radiograph shows early rib-notching involving the posterior portions of the third, fourth, and fifth ribs bilaterally. There is a "figure-three" sign in the left upper mediastinum, as a result of the aortic arch, and the poststenotic dilation of the aorta below the coarctation.

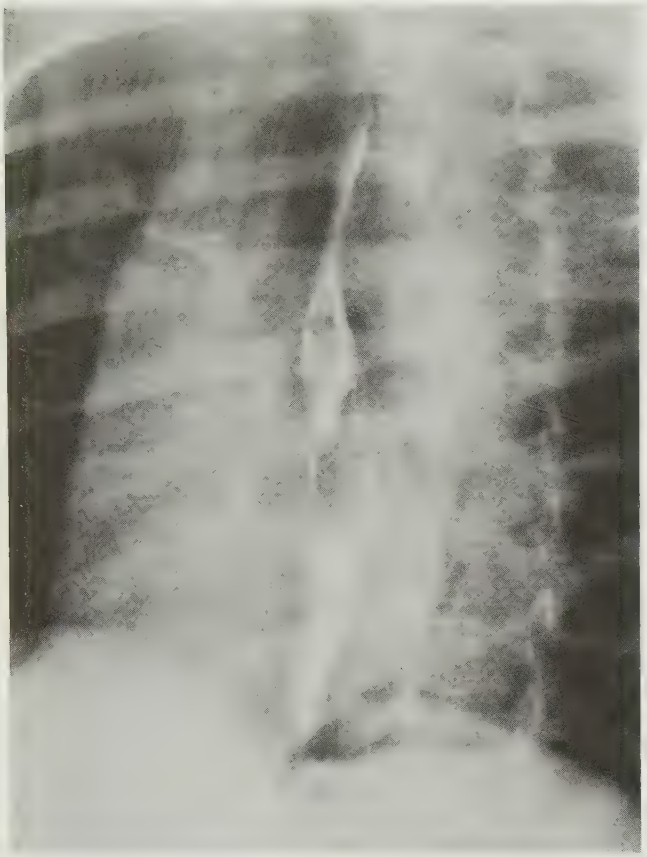

Fig. 44–27. Anterior oblique view in a normal child showing minimal indentation of the posterior portion of the esophagus by the aortic arch.

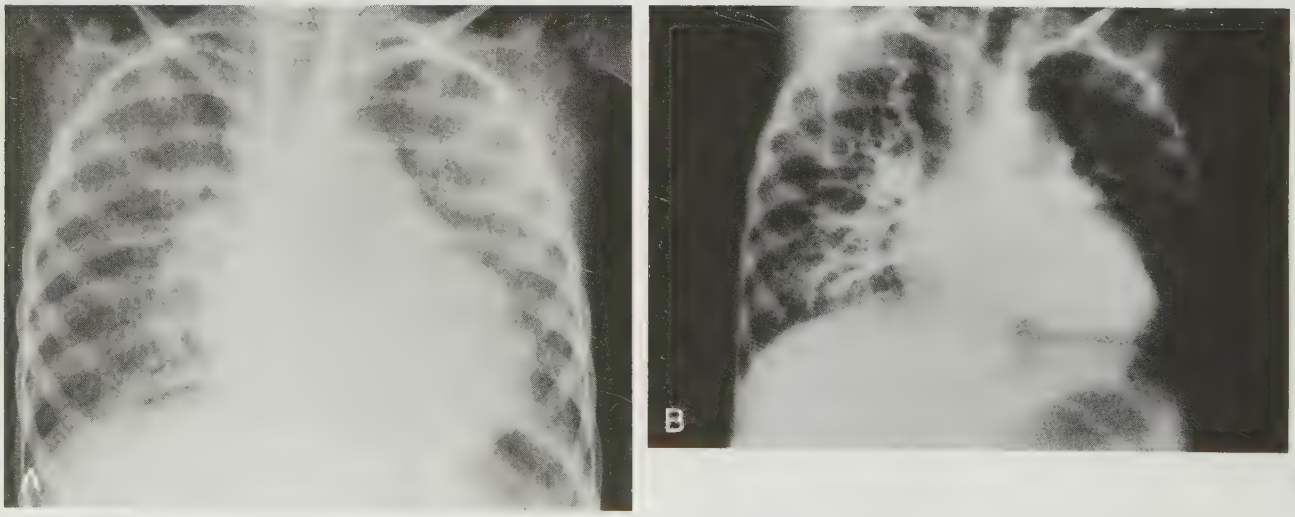

Fig. 44–28. Cor triatriatum. (A) The heart is slightly enlarged. Pulmonary arterial markings are normal, but there is an increase in the pulmonary venous pattern and faint Kerley B lines are identified above the costophrenic sulci. (B) Angiocardiogram shows the septum within the left atrium.

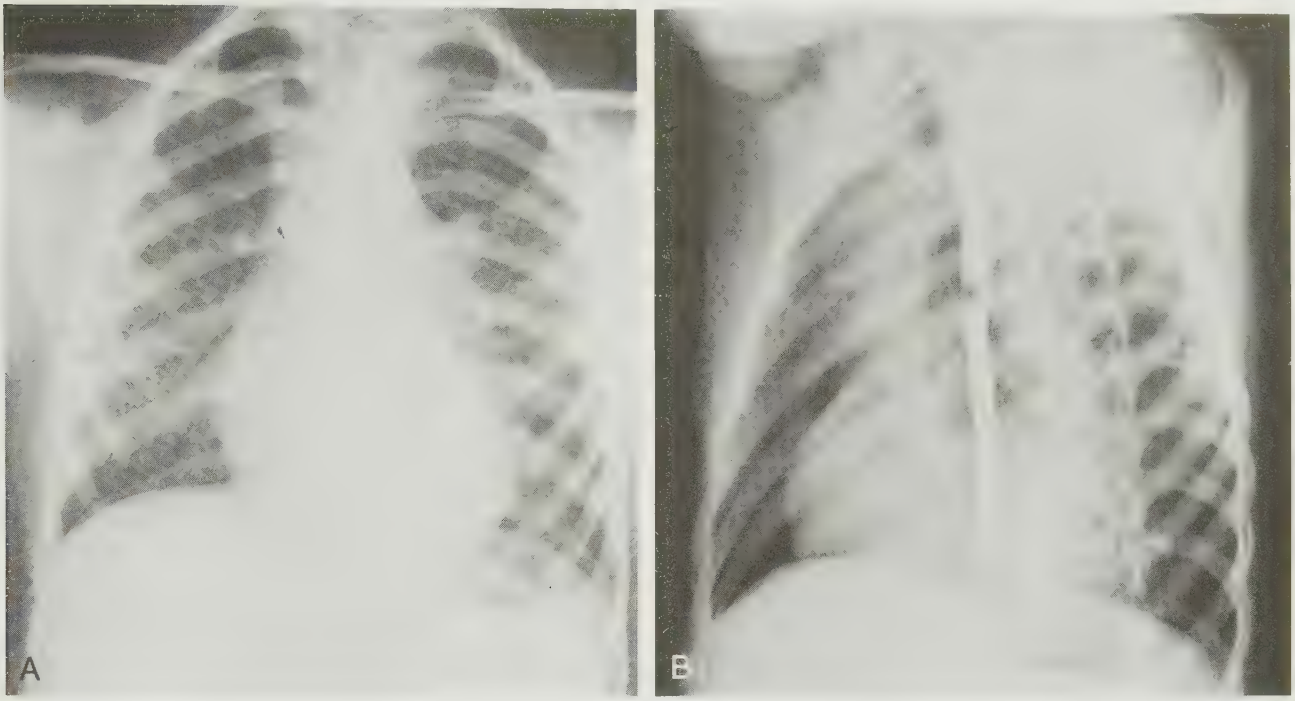

Fig. 44–29. Pure pulmonary valvular stenosis. (A) The heart is normal in size. The main pulmonary artery is abnormally convex, and the pulmonary arteries are within normal limits. (B) Left anterior oblique view shows increased convexity of the anterior chamber (right ventricle).

absence of pleural effusion and pneumothorax; and the location of the endotracheal tube, chest tubes, central lines, and pacemaker wires. Special attention also should be given to identifying any possible foreign object such as a surgical needle which may have been left inadvertently in the chest. Ideally, the endotracheal tube should be above the carina but below the thoracic inlet. An endotracheal tube that extends to or into the right main stem bronchus may produce hyperinflation of the right lung and atelectasis of the left lung. The chest tube should be inserted far enough to ensure that the holes in the tube are within the chest cavity. A central line placed in the neck should extend into the superior vena cava or into the right atrium. A Swan-Ganz catheter used for pulmonary artery pressure measurement usually passes into the right pulmonary artery where it can be advanced distally for purposes of measuring wedge pressures. It is also acceptable for the catheter to enter the left pulmonary artery. The pulmonary artery bifurcation is usually identifiable at the convexity of the main left pulmonary artery on the left cardiac border below the level of the aortic arch. However, in cases of left ventricular preponderance, the undivided segment may be in a more midline position and not be part of the left cardiac profile. The point of origin of the right and left pulmonary arteries may, consequently, be obscured. But the direction of the catheter to the right or left identifies the bifurcation.

The position of temporary pacing wires should be verified. Following removal of the endotracheal tube, another postoperative examination should be obtained—again, to evaluate cardiac size, pulmonary expansion, and the presence or absence of pleural effusion. The level of the diaphragm should be studied carefully after extubation in view of the possibility of phrenic nerve injury and diaphragmatic paralysis. Following removal of chest tubes, another portable chest radiograph is needed to ascertain that pneumothorax has not developed. A common complication of open heart surgery is the postpericardiotomy syndrome usually manifest within 1 to 3 weeks postoperatively. The radiographic findings in this condition include an increase in heart size secondary to pericardial effusion. Pleural effusion is also frequently present.

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CHAPTER 45

Electrocardiography

Arthur Garson, Jr

"There are comparatively few people who are not in greater danger of having their peace and happiness destroyed by an erroneous diagnosis of cardiac abnormality based on a faulty interpretation of an electrocardiogram than of being injured or killed by an atomic bomb." Thus began Frank Wilson's introduction to Lepeschkin's *Modern Electrocardiography,* over 30 years ago.[1] The same holds true today. Because it is so important to understand the basis and range of normal, the first half of this chapter is devoted to the normal electrocardiogram, the definition and proper measurement of electrocardiographic wave forms, and finally the variations produced by malposition of the heart within the thorax. In the second half of the chapter the abnormal electrocardiogram is considered. Since electrocardiography provides both complementary and supplementary information to echocardiography and nuclear imaging in terms of cardiac chamber enlargement and hypertrophy, we will consider the continuing contribution of the electrocardiogram in this area. The specific morphology of ventricular depolarization and repolarization will be shown to provide information on conduction disturbance, myocardial ischemia, injury, and infarction. The effect of systemic alterations on the electrocardiogram will be discussed: electrolyte abnormality, drug effects, and the effect of diseases in other parts of the body on the heart. Finally, a systematic approach to the recognition of artifacts will be presented in the hope that the patient with a normal heart will not become an "electrocardiographic casualty" because of an erroneous interpretation of what is truly sinus rhythm. This chapter is a synopsis of a book on the subject by Surawicz.[2] The interested reader can find greater detail, including a discussion of arrhythmias, in that volume.

THE NORMAL ELECTROCARDIOGRAM

As the transition is made from fetus to neonate, infant, child, and adult, changes in physiology, changes in size and position of the cardiac chambers relative to one another, changes in size and position of the heart relative to the body, and changes in overall body habitus, contribute to the different patterns of normal in the pediatric electrocardiogram. The major changes in amplitudes and direction of depolarization and repolarization occur in the first year of life; thereafter changes slowly occur in the timing of cardiac events, as reflected in the electrocardiographic intervals. Since the majority of the measurements made on a neonate's electrocardiogram would be abnormal in an adult (Fig. 45–1), it is important to refer to the table of normal values (see Table 45–1), which is given by age. In the following discussion, we will consider the normal electrocardiogram from the full-term newborn through the adolescent. Discussion of the normal premature[3] and adult[4] electrocardiograms can be found elsewhere.

Normal Values

Normal values included in Table 45–1 are those collected and published by Davignon et al.[5] These are summarized here; full tables can be found elsewhere.[2,5] This population consisted of 2141 white children. Each had a normal physical examination. The total population was divided into 12 age groups, with seven age groups in the first year of life to reflect the greater changes in the electrocardiogram during this time. There are at least 100 children in each age group. The data were analyzed by computer. In addition, the electrocardiograms that fell in the upper or lower tenth per-

Table 45–1. Summary of Normal Values

Age Group	Heart Rate (beats/min)*	Frontal Plane QRS Vector (degrees)	P–R Interval (sec)	QRS Duration V_5	Q III (mm)†‡	Q V_6 (mm)†	RV_1 (mm)	SV_1 (mm)	R/S V_1	RV_6 (mm)	SV_6 (mm)	R/S V_6	SV_1+RV_6 (mm)†	R+S V_4 (mm)†
Less than 1 day	93–154 (123)	+59 to −163 (137)	0.08–0.16 (.11)	.03–.07 (.05)	4.5	2	5–26 (14)	0–23 (8)	.1–U (2.2)	0–11 (4)	0–9.5 (3)	.1–U (2.0)	28	52.5
1 to 2 days	91–159 (123)	+64 to −161 (134)	0.08–0.14 (.11)	.03–.07 (.05)	6.5	2.5	5–27 (14)	0–21 (9)	.1–U (2.0)	0–12 (4.5)	0–9.5 (3)	.1–U (2.5)	29	52
3 to 6 days	91–166 (129)	+77 to −163 (132)	0.07–0.14 (.10)	.03–.07 (.05)	5.5	3	3–24 (13)	0–17 (7)	.2–U (2.7)	.5–12 (5)	0–10 (3.5)	.1–U (2.2)	24.5	49
1 to 3 wk	107–182 (148)	+65 to +161 (110)	0.07–0.14 (.10)	.03–.08 (.05)	6	3	3–21 (11)	0–11 (4)	1.0–U (2.9)	2.5–16.5 (7.5)	0–10 (3.5)	.1–U (3.3)	21	49
1 to 2 mo	121–179 (149)	+31 to +113 (74)	0.07–0.13 (.10)	.03–.08 (.05)	7.5	3	3–18 (10)	0–12 (5)	.3–U (2.3)	5–21.5 (11.5)	0–6.5 (3)	.2–U (4.8)	29	53.5
3 to 5 mo	106–186 (141)	+7 to +104 (60)	0.07–0.15 (.11)	.03–.08 (.05)	6.5	3	3–20 (10)	0–17 (6)	.1–U (2.3)	6.5–22.5 (13)	0–10 (3)	.2–U (6.2)	35	61.5
6 to 11 mo	109–169 (134)	+6 to +99 (56)	0.07–0.16 (.11)	.03–.08 (.05)	8.5	3	1.5–20 (9.5)	.5–18 (4)	.1–3.9 (1.6)	6–22.5 (12.5)	0–7 (2)	.2–U (7.6)	32	53
1 to 2 yr	89–151 (119)	+7 to +101 (55)	0.08–0.15 (.11)	.04–.08 (.06)	6	3	2.5–17 (9)	.5–21 (8)	.05–4.3 (1.4)	6–22.5 (13)	0–6.5 (2)	.3–U (9.3)	39	49.5
3 to 4 yr	73–137 (108)	+6 to +104 (55)	0.09–0.16 (.12)	.04–.08 (.06)	5	3.5	1–18 (8)	.2–21 (10)	.03–2.8 (.9)	8–24.5 (15)	0–5 (1.5)	.6–U (10.8)	42	53.5
5 to 7 yr	65–133 (100)	+11 to +143 (65)	0.09–0.16 (.12)	.04–.08 (.06)	4	4.5	.5–14 (7)	.3–24 (12)	.02–2.0 (.7)	8.5–26.5 (16)	0–4 (1)	.9–U (11.5)	47	54
8 to 11 yr	62–130 (91)	+9 to +114 (61)	0.09–0.17 (.13)	.04–.09 (.06)	3	3	0–12 (5.5)	.3–25 (12)	0–1.8 (.5)	9–25.5 (16)	0–4 (1)	1.5–U (14.3)	45.5	53
12 to 15 yr	60–119 (85)	+11 to +130 (59)	0.09–0.18 (.14)	.04–.09 (.07)	3	3	0–10 (4)	.3–21 (11)	0–1.7 (.5)	6.5–23 (14)	0–4 (1)	1.4–U (14.7)	41	50

*2 to 98% (mean)
†Ninety-eighth percentile
‡Millimeters at normal standardization
§Undefined (5 may equal zero)

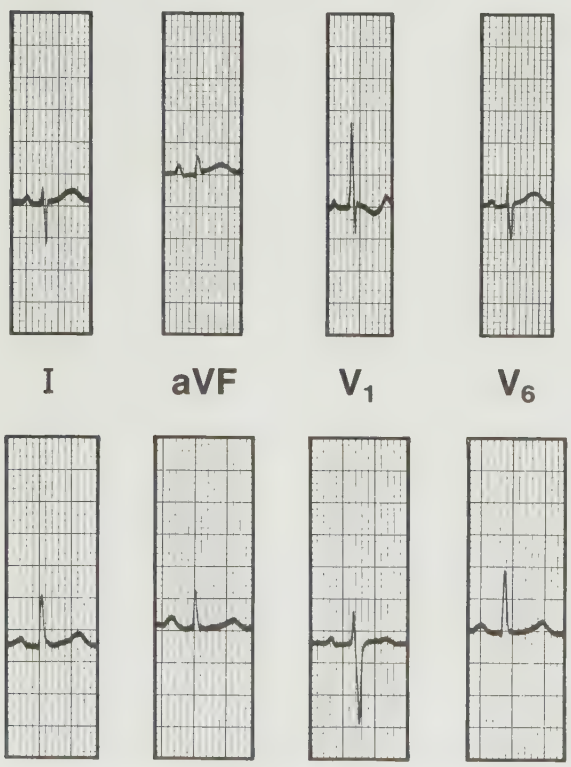


Fig. 45–1. Comparison of the normal neonatal and adolescent electrocardiogram. The neonate is shown in the top row and the adolescent in the bottom row.

centile were displayed with an electrocardiograph and were verified visually by a physician. If the computer and physician disagreed, the visually determined value by the physician was substituted in the data file. These normal values are therefore applicable to all tracings recorded from an electrocardiograph that meets American Heart Association standards. The limits of "normal" include the second and ninety-eighth percentile in each age range.

Heart Rate

In sinus rhythm, the heart rate is measured by determining the interval between successive P waves or R waves on the electrocardiogram. The onset of each deflection should be used for timing rather than the peak since a change in the shape of a complex may result in a faulty measurement if the peak occurs at a different time relative to the beginning of the complex (Fig. 45–2). The exact heart rate can be calculated by dividing the RR intervals (in seconds) into 60. For example, assume an RR interval of 0.46 sec; the heart rate is 60/0.46 or 130 beats/min. An approximation can be made by counting the number of 0.2-sec blocks (large boxes on the electrocardiogram paper) that are contained in the RR interval. If the RR interval is approximately one box (0.2 sec), the heart rate is 300 beats/min; for two boxes, it is 150 beats/min; and so on: 300, 150, 100, 75, 60, 50, 43, 38. For a more exact heart rate, it is helpful to remember that the small boxes (0.04 sec) between 100 and 150 represent 10 beats/min and those between 150 and 300 represent 30 beats/min (Fig. 45–3). This can be committed to memory.

The normal heart rate increases from the first day of life to a maximum between 1 and 2 months of age and then slowly declines (see Table 45–1). The reason for this has not been demonstrated but probably is connected to the relative immaturity of the sympathetic nervous system at birth.

P Wave

The configuration of the P wave is generally symmetric in leads I and II. The normal shape is that of a bullet, and not of a steeple

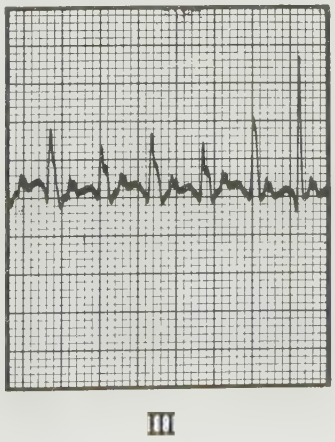


Fig. 45–2. Measurement of heart rate. In this patient with supraventricular tachycardia with varying intraventricular conduction, the QRS morphology changes sufficiently that the peak of each complex does not occur at the same time relative to the onset of each beat. Therefore in measuring heart rate, rather than measuring from peak to peak, the onset of the QRS complex should be used at all times.

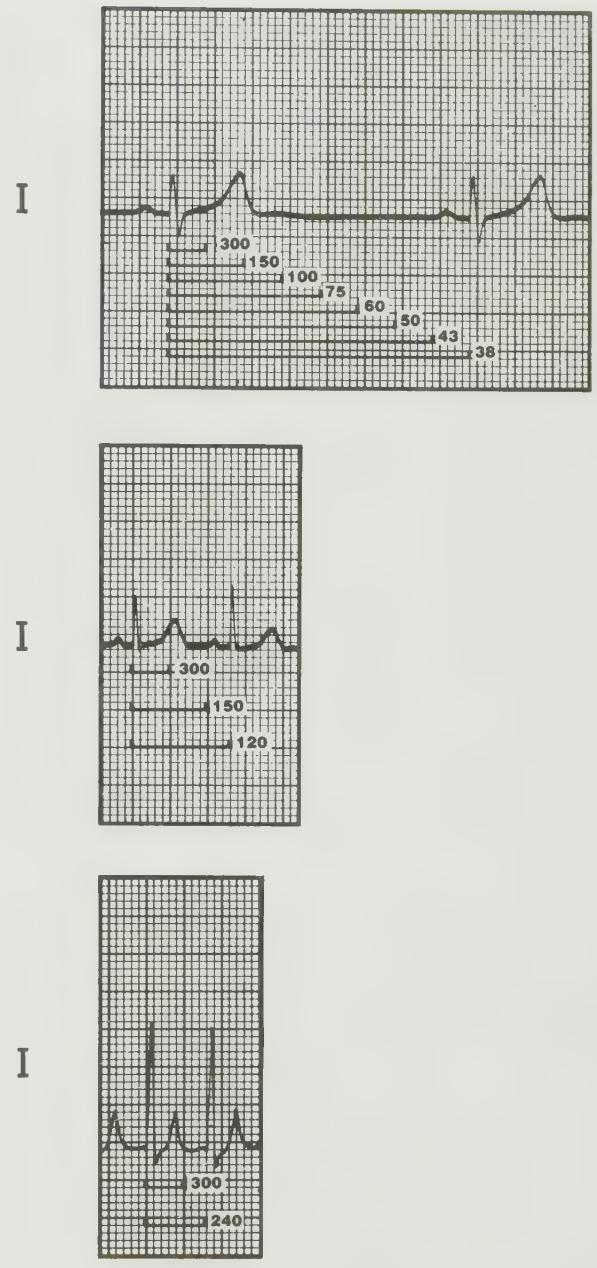


Fig. 45–3. Calculation of heart rate. Top tracing—a heart rate of 38 beats/min. This is exactly nine large boxes on the electrocardiogram. The method of counting large boxes is illustrated. Middle tracing—sinus rhythm at a rate of 120 beats/min. The QRS complexes are separated by two large boxes and three small boxes. Lower tracing—supraventricular tachycardia at 240 beats/min. The QRS complexes are separated by one large and three small boxes.

(right atrial enlargement) or a bent staple (left atrial enlargement) (Fig. 45–4). With the improved frequency response of most electrocardiographic machines, over 25% of normal children will have a notch in the middle of the P wave. Therefore notching by itself must be considered normal. In lead V_1, the P wave may normally be biphasic, but the terminal negative portion should be less than 0.04 sec in duration and less than 1 mm deep (less than one small box by one small box). The overall duration of the P wave in lead II should be between 0.03 and 0.09 sec in children 3 years old and younger; over the age of 3 years, the normal duration is between 0.05 and 0.10 sec. The normal P wave amplitude is less than 2.5 mm at all ages.

The P wave axis is directed away from the site of origin of atrial depolarization. (The more proper term for "axis" is "mean vector"—but the more popular term will be used.) While it is possible to calculate the exact P-wave axis in practice only the quadrant of the vector in the frontal plane is determined. If the P wave is isoelectric or positive in lead I and isoelectric or positive in lead aVF (P-wave mean vector between 0° and +90°), we infer that the atria begin depolarization from the high right atrium, i.e., from the sinus node (Fig. 45–5). If the P wave is negative in lead aVF and isoelectric or positive in lead I (P-wave axis between −1° and −90°), the atria begin depolarization from the low right atrium. If the P wave is negative in lead I (P-wave axis between +91° and −91°), the atria begin depolarization from the left atrium (see section on "Malposition of the Heart"). The P-wave axis in the horizontal plane is variable and is not helpful in determining the site of origin of atrial depolarization, i.e., sinus P waves can be positive, isoelectric, or negative in lead V_1.

P–R Interval

The P–R interval is measured from the beginning of the P wave to the beginning of the QRS complex. The true onset of atrial or ventricular depolarization may not be recorded in a lead because the initial forces are directed perpendicular to the lead and the initial portion of the P wave or QRS complex may therefore be isoelectric in that lead. Thus the P–R intervals measured in different leads may vary by as much as 0.04 sec (Fig. 45–6), but usually only vary by 0.02 sec or less.[4] It has been the practice to measure either the longest P–R interval or the P–R interval in lead II. Standards are available in children only for lead II (see Table 45–1). If a "delta wave" is present (see section on "Preexcitation"), the shortest "P–R interval" (actually a P–delta interval) should be sought in the diagnosis of the Wolff-Parkinson-White syndrome. With an isoelectric delta wave, the P–R interval may be normal, and only in certain leads will the truly short P–R interval be observed (Fig. 45–7). (See section on "Preexcitation" for other causes of short P–R interval.) A more common cause for a short P–R interval in a normal heart is a low right atrial pacemaker. In this instance, the P wave is negative in lead aVF and positive or isoelectric in lead I. When the impulse originates low in the atrium, the normal high to low right atrial conduction time (which accounts for up to 0.04 sec of the P–R interval) is eliminated, and therefore low right atrial pacemakers may have a P–R interval up to 0.04 sec less than normal.

The P–R interval normally increases with age and decreases with heart rate. The increase in P–R interval with decreased heart rate can be accounted for by the fact that heart rate decreases normally with age. Therefore in Table 45–1, the P–R interval is correlated with age and not heart rate.

P–R Segment

The P–R segment is measured from the end of the P wave to the beginning of the QRS complex. The length of this segment is variable and depends upon the duration of the P wave. Normal

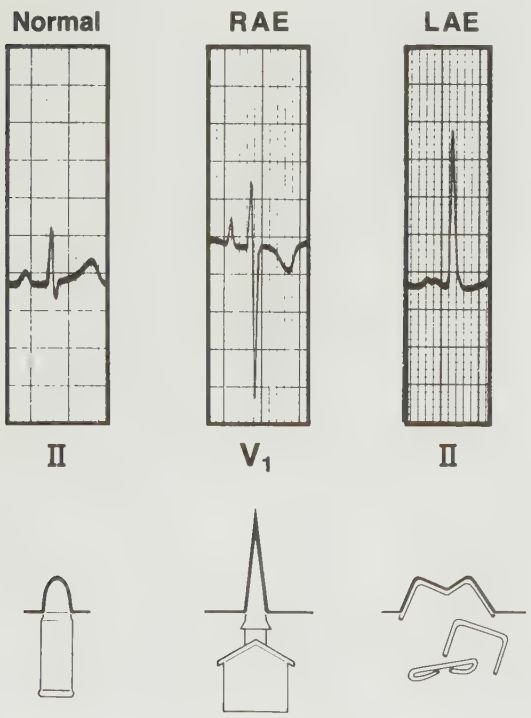


Fig. 45–4. Shape of P wave. On the left, the normal shape is shown to be similar to that of a bullet. In the middle, the P wave of right atrial enlargement (RAE) is shown. This is similar to a church steeple. On the right, the P wave of left atrial enlargement (LAE) is shown. This is similar to a bent staple.

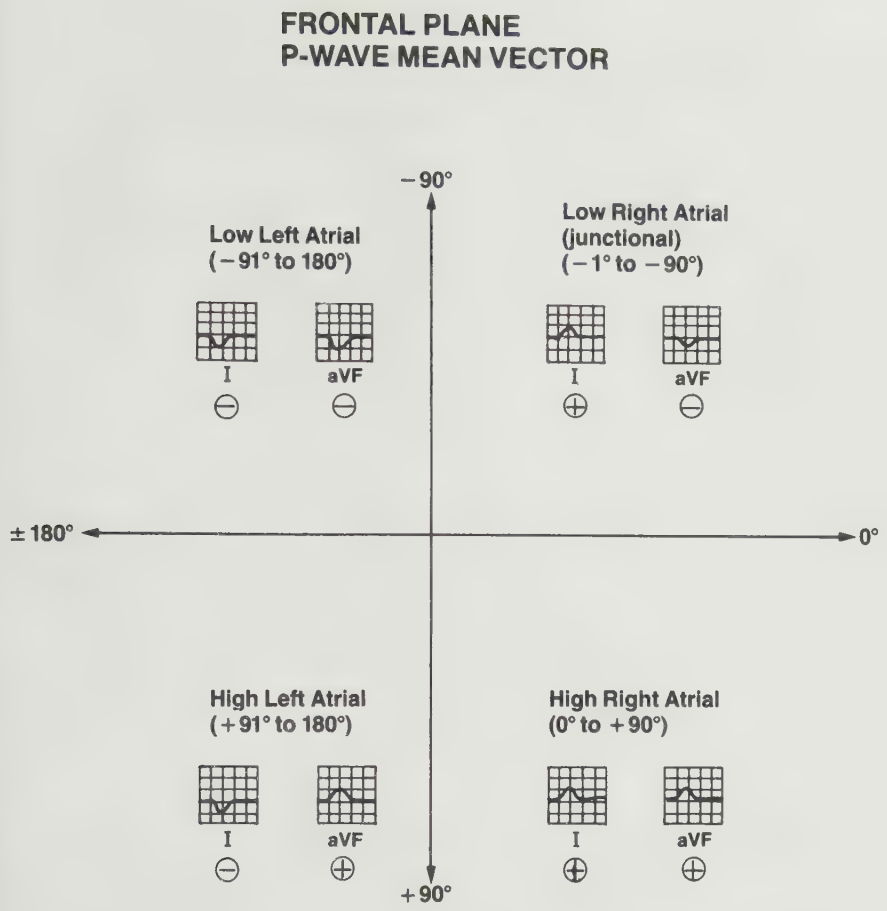


Fig. 45–5. Frontal plane P-wave mean vector (axis).

values for the duration of the P–R segment in children are not available. A short P–R segment is most often due to a long P wave with a normal P–R interval, rather than to the Wolff-Parkinson-White syndrome. The importance of the P–R segment in pediatrics is that it may provide the only estimation of the isoelectric line on the electrocardiogram.

QRS Complex

Duration

The QRS duration is measured from the beginning to the end of the ventricular depolarization complex. It should be measured in a lead with a Q wave. The precordial leads may have a QRS duration that is 0.01 to 0.02 sec longer than that measured in the limb leads.[4] For the normal values included in Table 45–1, lead V_5 was chosen to measure the duration because there usually is a Q wave and a defined termination to the QRS complex. As ventricular muscle mass increases, the QRS duration increases. Since with age, the muscle mass increases, the QRS duration tends to increase with age.

Axis

The most practical method for estimation of the axis is to determine the most isoelectric complex (Fig. 45–8). This is defined as the lead in which the sum of positive and negative deflections equals 0. The QRS mean vector is perpendicular to this lead. However, there are two possible perpendiculars. For example, if lead aVR is isoelectric, this implies that the axis is directed 90° away from (perpendicular to) lead aVR. Since lead aVR points toward −150°, the axis would be directed toward either −60° or +120°. To determine which of the two perpendiculars is the true axis, the lead with the maximum net positive deflection is examined. If lead III has the maximum net positive deflection, the frontal plane QRS axis is +120°. It is more accurate to base the calculation of the perpendicular to the isoelectric lead rather than simly on the direction of the largest deflection, because of the true difference in lengths of the lead axes. If all the QRS complexes in the frontal plane are equiphasic, the axis is termed "indeterminate" and no calculation can be made.

"Axis Deviation". If the value for the QRS axis falls outside the range of normal values for age (see Table 45–1), "axis deviation" is diagnosed. In the first month of life, "right-axis deviation" occurs when the axis is between the upper limit for age and −90° ("northwest axis"). In older children, right axis deviation occurs when the axis is between the upper limit for age and ±180°. For a 3-mo-old, right-axis deviation is between +105° and +180°. In a 10-yr-old, right-axis deviation is between +120° and +180° (Fig. 45–9). Using logic from the "method of perpendiculars," if the QRS complex is isoelectric or positive in lead aVR (and isoelectric and positive in lead aVF) in a 10-yr-old, right-axis deviation is diagnosed. The most common cause of right-axis deviation in children is right ventricular hypertrophy.

"Left-axis deviation" occurs when the axis is between the lower limit for age and −90°. Over the age of 2 mo, left-axis deviation

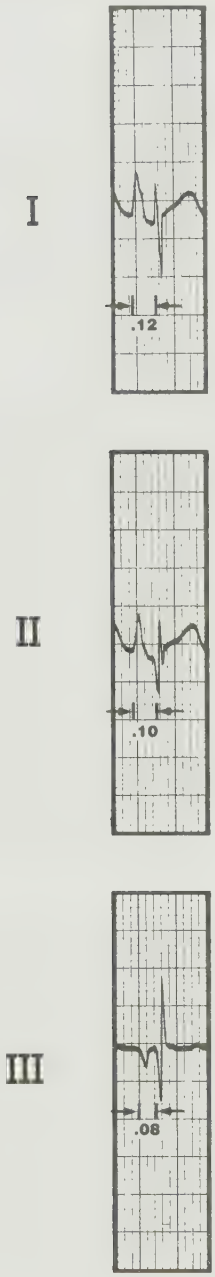


Fig. 45–6. P–R interval. Simultaneous leads I, II, and III. The P–R interval in lead I is 0.12 sec, in lead II 0.10 sec, and in lead III 0.08 sec. The reason for the seemingly short P–R interval in lead III is that the early part of the P wave is isoelectric in that lead.

is between 0° and −90° (Fig. 45–9). Using logic from the method of perpendiculars, if the QRS complex is isoelectric or negative in lead aVF (and isoelectric or positive in lead I), in a child over 2 mo of age, left-axis deviation is diagnosed. The most common causes of left-axis deviation in childhood are those due to abnormal intraventricular conduction associated with congenital heart disease: complete atrioventricular canal, ostium primum atrial septal defect, tricuspid atresia, single ventricle (see section on "Left Anterior Hemiblock"). Concentric left ventricular hypertrophy generally does not cause left-axis deviation.

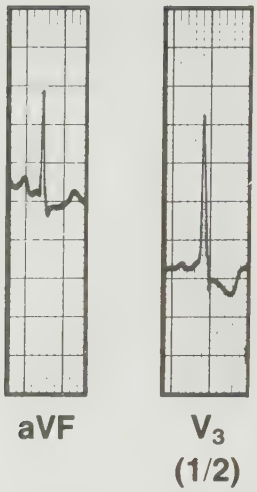


Fig. 45–7. P–R interval in Wolff-Parkinson-White syndrome. In lead aVF, the P–R interval is normal and there is no delta wave. The short P–R interval and delta wave are apparent only in lead V_3, taken from the same patient.

If the frontal plane QRS axis is between −90° and ± 180°, "northwest axis" is diagnosed (Fig. 45–9). This may be either an extreme form of right-axis or left-axis deviation. In general, in northwest axis only, if the initial QRS forces are directed at +120° (Q wave in lead I or aVL), left anterior hemiblock coexists with the northwest axis and this is a form of extreme left axis deviation. On the other hand, if the initial forces are directed at −60° (Q waves or QRS pattern in leads II, III, and aVF) this is extreme right-axis deviation.

Morphology

Depending upon the lead and orientation of the initial forces, a Q wave may or may not be present. The remainder of ventricular depolarization is written as an R wave followed by an S wave. This is true in all normal precordial leads and limb leads other than lead aVR, with the following exception. An R wave without an S wave may be present normally in lead V_1 up to 5 mo of age and in lead V_6 at any age. In approximately 7% of normal children, in the right chest leads, a second R wave or R′ may follow the S wave, giving an RSR′ pattern.[6] In these normal children, the overall QRS duration may be prolonged by 0.01 sec above the normals given in Table 45–1, but the R′ wave has a rapid deflection and has the same duration as the preceding R and S waves. In normal children, wih an RSR′ pattern, the S wave usually has a greater amplitude than either the R or R′ wave. The RSR′ pattern can be found in complete right bundle branch block and right ventricular hypertrophy. In complete right bundle branch block,

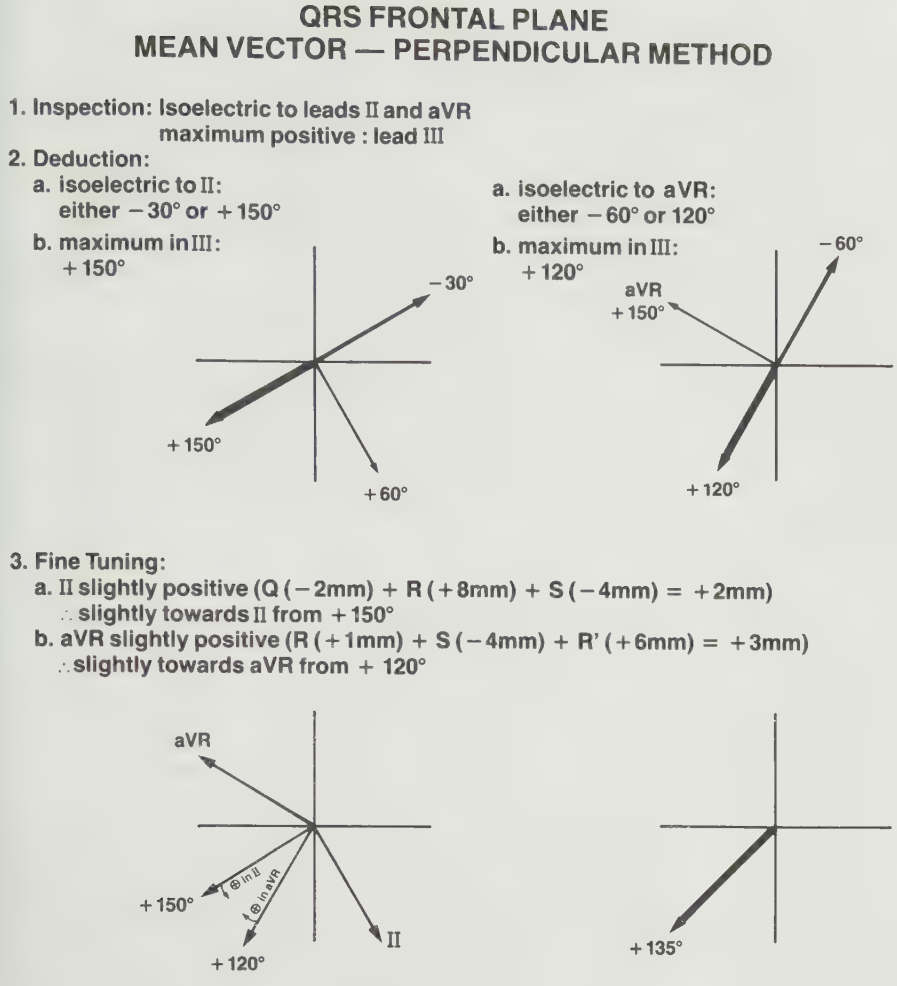


Fig. 45–8. Calculation of QRS frontal plane mean vector (axis) by the perpendicular method (see text).

the total QRS duration is increased and there is a true terminal conduction delay with an increase in the duration of the slurred R′ as compared with the normal duration of the initial R and S waves (see section on "Conduction Disturbance"). In mild to moderate right ventricular hypertrophy, the R and especially the R′ waves have a greater amplitude than the S wave. With a QRS complex of normal duration, right ventricular hypertrophy can be diagnosed by an R′ amplitude greater than 15 mm in an infant under 1 year of age or 10 mm over 1 year. In children with a QRS complex of normal duration and an RSR′ pattern with a small R′ wave, since the distinction between mild to moderate right ventricular hypertrophy, incomplete right bundle branch block, and normal is difficult, we would prefer the designation "RSR′ pattern in right chest leads" without a further attempt at diagnosis.

Amplitude

Q Wave. A normal Q wave may be present in almost any lead. A QS pattern (or initial S wave) may be normal in lead aVR at any age and in V_3R and V_4R in older children. A QR pattern (Q wave followed by an R wave) is not normal in lead aVR or the right chest leads, and if present, this usually indicates right ventricular hypertrophy (see section on "Right Ventricular Hypertrophy"). Q waves present in the midprecordial leads generally imply counterclockwise rotation of the heart (see section on "Malposition of the Heart").

The distinguishing points between normal and abnormal Q waves are the duration and the amplitude of the Q wave. A normal duration Q wave is 0.01 to 0.015 sec. Any Q wave greater than 0.03 sec is definitely abnormal.[6,7] The normal amplitude of Q waves varies with the lead and with age.[5] Normal for lead aVL is less than 2 mm; lead I less than 3 mm; and leads II and aVF less than 4 mm. At all ages leads III and V_6 are the most variable with age (see Table 45–1).[8] The implications of abnormal Q waves are further discussed in the section on "Infarction."

R and S Waves. Since in the frontal plane, the ventricles overlie each other to a great extent, the attempt at separation of right ventricular from left ventricular forces is best made in the horizontal plane. Therefore R-wave and S-wave amplitude will only be considered in the horizontal plane. In the normal heart with normally related ventricles, the right ventricular forces are directed anteriorly and to the right. The anterior forces are reflected by the height of the R wave in lead V_1 and the rightward forces by the depth of the S wave in lead V_6. Conversely, the posterior forces

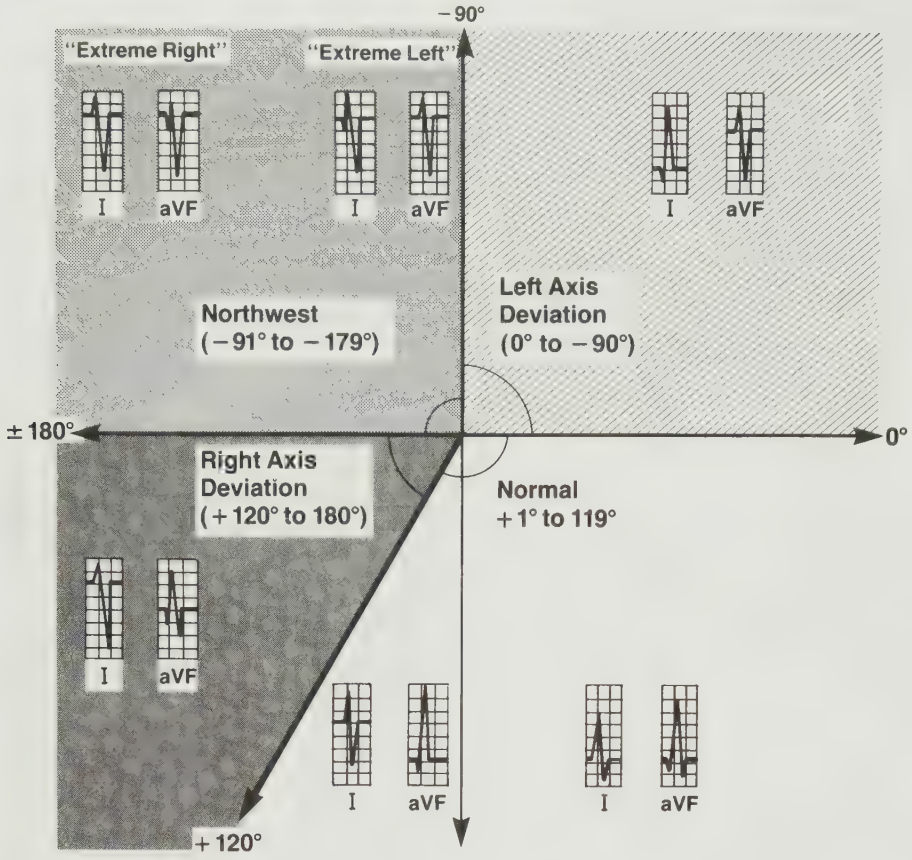


Fig. 45–9. "Axis deviation." Limits for normal and abnormal frontal plane axis in a 10-year-old child. The electocardiograms have been drawn to reflect the mean vector in each of the quadrants.

generated by the left ventricle are reflected by the depth of the S wave in lead V_1 and the leftward forces generated by the left ventricle are reflected by the height of the R wave in lead V_6. Left ventricular forces can also be represented by the sum of the posterior and leftward forces, or the sum of the depth of the S wave in lead V_1 plus the height of the R wave in lead V_6. The normal values by age for the amplitudes and ratios of R waves and S waves in leads V_1 and V_6 are given in Table 45–1.

The transition leads are the precordial leads in which the QRS complexes are approximately equiphasic (R and S waves are equal amplitude). The transition leads record activity from both ventricles and if the total amplitude of the R wave plus the S wave in the transition leads is increased, this represents biventricular hypertrophy. In Table 45–1 the normal total amplitude of R plus S in lead V_4 is given.

The mean amplitudes of the waves reflecting the right ventricle decrease with age while those reflecting the left ventricle increase with age. The variability of these amplitudes also decreases with age. During adolescence (12 to 16 years of age) sex differences in the electrocardiogram become manifest. R waves, especially in the left chest leads, are smaller in girls. This may represent breast development or the smaller cardiac size in women. With adolescence, changes in race and body habitus become more manifest. Larger midprecordial voltages are found in blacks and those with thin chests.[9]

Lower Limit of QRS Amplitude

Heretofore, we have been concerned with the upper limits for QRS amplitude. The lower limit is important because low-voltage QRS complexes are usually a sign of myocardial edema (in myocarditis, myxedema or generalized edema), loss of functioning myocardium (in congestive heart failure, tumor, or amyloid), or increased distance between the heart and chest wall (in obesity, pneumothorax, constrictive pericarditis, or pericardial or pleural effusion) (see section on "Injury due to Myocarditis"). The criterion for abnormally low voltage of QRS complexes is a total amplitude of R + S or 5 mm or less in each of the limb leads or 8 mm or less in each of the chest leads.[7]

ST Segment

The ST segment is the portion of the electrocardiogram between the end of the S wave and the beginning of the T wave. The ST segment normally gently curves into the proximal limb of the T wave and is not perfectly horizontal. To determine ST-segment deviation above or below the base line, it is best to consider the P–R segment as the base line (see section on "P–R Segment"). The ST segments should not be elevated to more than 1 mm or depressed greater than 0.5 mm in any lead in children. The exception is the "early repolarization" syndrome of adolescence, in which the ST segment can be elevated to 4 mm in the midprecordial leads (see section on "Functional T-Wave Changes").

The T Wave

The T wave is normally asymmetrical in shape with the upstroke having a more gradual slope than the downstroke (Fig. 45–10A). The T wave usually has a smooth, curved form but it may have a notch near its summit (Fig. 45–10B).

The T-wave amplitude is generally not measured in specific

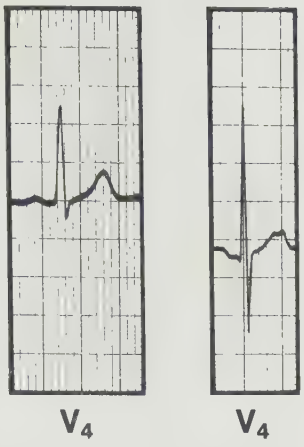


Fig. 45–10. T waves. (A) Normal smooth T wave. (B) Normal notched T wave.

leads, since it is so variable in normal children. However, low-voltage or "flattened" T waves in several leads may indicate an abnormality (see section on "Ischemia"). The T waves in leads I, II, and V_6 should be more than 2 mm in all children over 48 hr old. An abnormally tall T wave is generally defined at any age as greater than 7 mm in a limb lead or 10 mm in a precordial lead.

The T-wave axis in the frontal plane can be calculated by the same methods as for the QRS complex. However, in practice it is helpful to remember that in normal children the T waves should be upright in leads I and II (over 48 hours of age), upright in lead aVF (over 5 days of age), and inverted in lead aVR (at all ages) (Fig. 45–11). Between approximately 5 days of age and adolescence, the T waves should be inverted in leads V_1 and V_3R.[10] If they are positive, this is usually a sign of right ventricular hypertrophy. In infants less than approximately 5 days of age or in adults, the T waves in lead V_1 or V_3R are variable. The T waves in lead V_6 should be positive at all ages.

The U Wave

The normal U wave has the same polarity as the preceding T wave but the normal U wave has only 2 to 24% of the T-wave amplitude. There is a wide variation of normal; however, the normal U wave should not be more than 50% of the amplitude of the T wave (Fig. 45–12). The largest-amplitude U waves are recorded in leads V_2 to V_4. The shape of a normal U wave is different from the normal T wave. In the U wave, the upstroke is steeper than the downstroke.[7,11]

Differentiating T, U and P Waves

It is important to differentiate between T waves and normal U waves so that the U wave can be discounted in the measurement of the Q–T interval. A normal U wave is one with an amplitude no more than 50% of the preceding T wave. At slow heart rates, the T and U waves are usually separated by a distinct isoelectric line, but at rates over 90 beats/min, there may be no intervening isoelectric line and it may be difficult to determine whether the terminal portion of the deflection is a U wave or the second half of a notched T wave. If, in the same or a different lead, another wave is seen later in timing than the questionable wave, then the questionable wave is a notched T wave (Fig. 45–13). It may be possible to bring out a U wave by recording the electrocardiogram in the sitting position. This tends to decrease the T-wave and increase the U-wave amplitude in the left precordial leads.[12]

If there is a single wave in all leads, it is not possible to determine whether this represents a T wave or fusion of a T wave and U wave. If there is no notch in any lead, but the wave is smooth throughout, it should be considered a T wave (Fig. 45–14). If there is a notch in the terminal part of the wave and the amplitude is 50% or less of the peak, then the downstroke of the early portion of the wave should be extrapolated as the T wave (Fig. 45–15). If the terminal portion of the wave in any lead (usually V_4 is the clearest) is more than 50% of the amplitude of the peak, the terminal portion of the wave should be included as part of the T wave (Fig. 45–16). Whether this terminal portion should be called a T wave is semantic.[13] The important electrocardiographic ques-

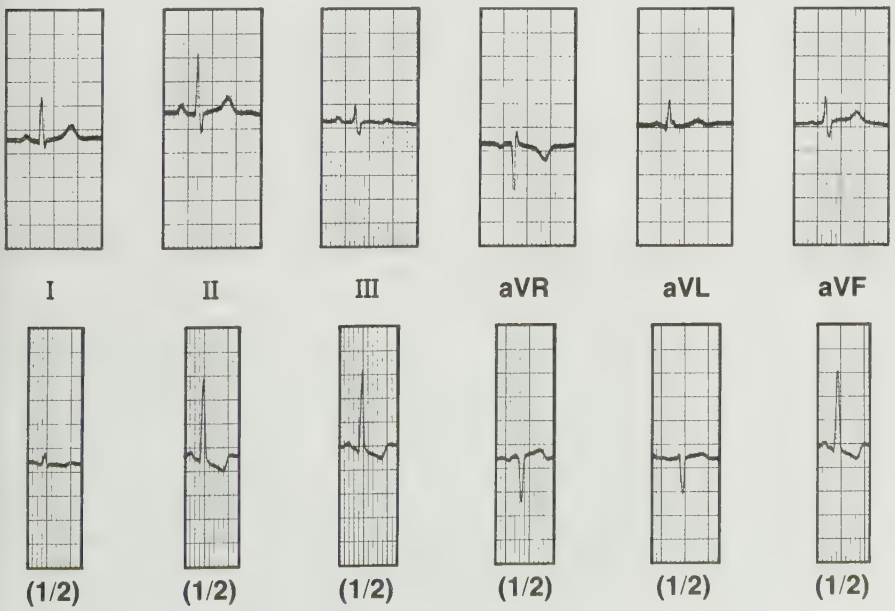


Fig. 45–11. T-wave axis. Top tracings: Normal 7-yr-old; QRS frontal plane axis +17°, T-wave axis +34°; the QRST angle is 17°. Bottom tracings: 7-yr-old with severe aortic stenosis; frontal plane QRS axis +85°, T wave axis −90°; the QRST angle is 175°.

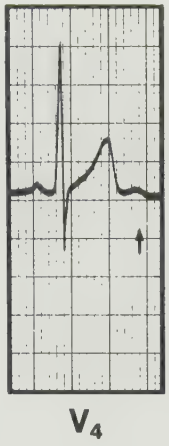


Fig. 45–12. U wave (arrow).

tion to be answered is whether there is a significant increase in the amount of late repolarization. This can be indicated either by a separate U wave with an amplitude more than 50% of the T wave, or by a single fusion wave whose terminal portion is more than 50% of the amplitude of the peak. The causes and consequences of increased late repolarization are the same. Therefore the same consideration should be given to long T waves as to excessively large U waves.

The distinction of P waves from T or U waves in sinus rhythm is simplified by examining multiple leads. P waves are most obvious in lead II and least obvious in leads V_4 to V_7. T and U waves are most obvious in leads V_4 to V_7. Therefore a synthesis can be made of the different waves by using the timing from different leads (Fig. 45–17). In sinus tachycardia, the P wave may begin before the T wave has been completed. At rapid rates, P waves become much more pointed than T waves. Again, in leads V_6 or V_7 almost all of the wave is likely to be a T wave while in lead II, the maximum P wave is likely to be visible. In supraventricular tachycardia, the most pointed of the waves are P waves. P waves can also be identified as discrete deflections usually lasting 0.06 sec or less, which occur with an improper timing for a QRS complex or a T wave (Fig. 45–18). Using this type of analysis,

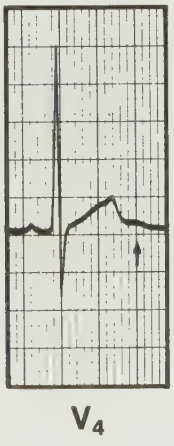


Fig. 45–13. Notched T wave followed by a U wave.

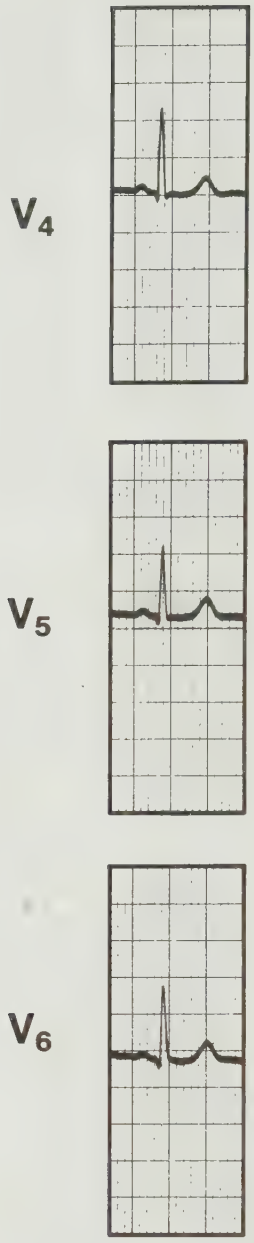


Fig. 45–14. There is no notch in any of the waves following the QRS complex and so these should all be considered T waves. Simultaneous leads V_4, V_5, and V_6.

we have found it possible to distinguish P waves in 55% of children during supraventricular tachycardia.[14]

Q–T Interval

The Q–T interval begins at the onset of the QRS complex and terminates at the end of the T wave. The longest interval in any lead should be used. As noted in the previous section, in certain conditions, it may be difficult to choose the proper end of the T wave. I agree with James[15] that "In electrocardiography, there is no more nebulous measurement than the Q–T interval," but some rules may be helpful (Fig. 45–19). 1) If a separate T and U wave are visible and the U-wave amplitude is 50% or less of the T-wave amplitude, the Q–T interval ends at the end of the T wave.

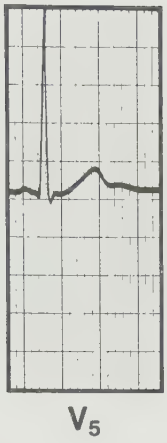


Fig. 45–15. T wave followed by a notch with an amplitude less than 50% of the peak of the T wave. In this case, the T wave is considered to have merged with the U wave and the T wave ends at the extrapolated downslope of the larger wave.

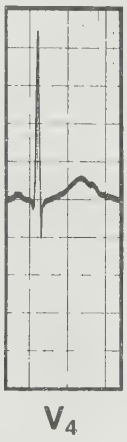


Fig. 45–16. T wave with a notch and the peak of the terminal segment is greater than 50% of the peak of the T wave. In this case, both of these waves should be considered as part of the T wave.

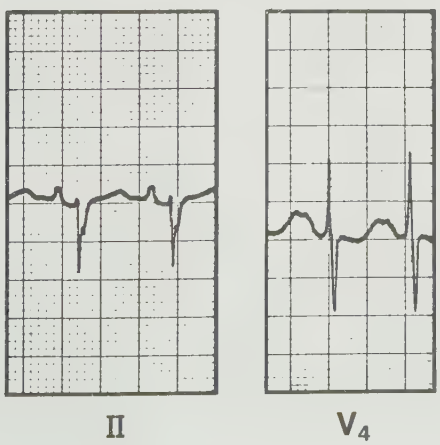


Fig. 45–17. Distinction of P waves from T waves. In lead V_4, it is not possible to tell whether these waves are merged P waves with T waves or T and U waves. It is apparent from examination of lead II in the same patient that the second notch in lead V_4 is caused by the P wave.

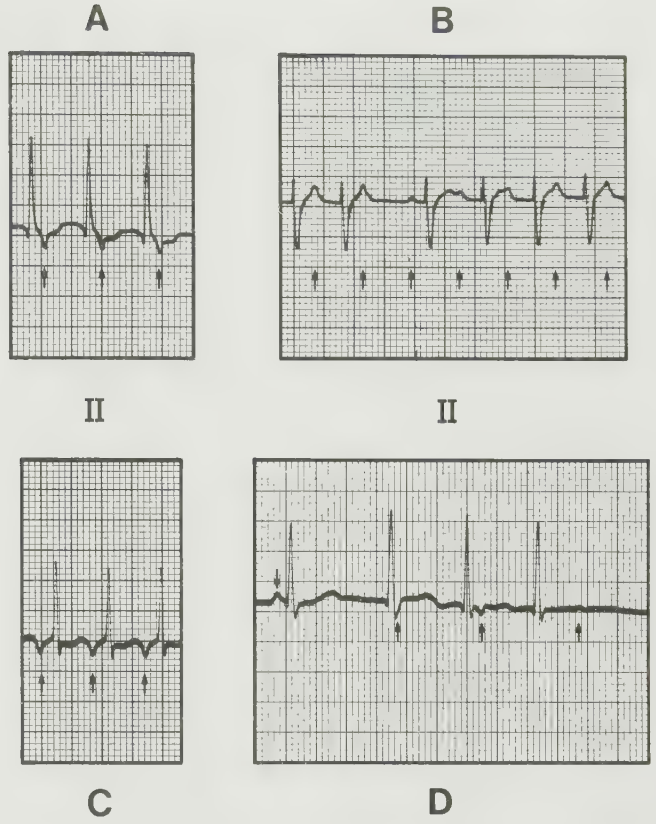


Fig. 45–18. Identification of P waves (arrows). (A) P waves in the early part of the ST segment. (B) P waves directly on top of T waves. The only way of distinguishing these waves was to observe an episode of spontaneous type I second-degree atrioventricular block in which the P wave was not followed by a QRS complex. This allowed observation of the P wave preceding the next QRS complex with a lengthening P–R interval in subsequent beats. (C) P waves on the downslope of the T wave. (D) P waves with differing relations to the QRS and T wave. In the second QRS complex, the widened S wave is caused by a superimposed P wave.

2) If a single wave is visible and there is no notch in any lead, the entire wave is included in the Q–T interval. 3) If a single wave is visible but a notch is present in the wave and the terminal portion of the wave has an amplitude of 50% or less of the peak, then the initial downslope should be extrapolated and the extrapolation used for the Q–T interval. 4) If a single wave is visible, has a notch, and the terminal portion has an amplitude of more than 50% of the peak, then the entire wave is included as the T wave. 5) If a P wave is superimposed, extrapolate the T wave back to the base line from the initial downstroke (see Fig. 45–19). The Q–T interval varies with heart rate. The Q–T interval can be corrected for heart rate by Bazett's (1918) formula: The corrected Q–T interval (Q–Tc) is equal to the Q–T interval (in seconds) divided by the square root of the R–R interval (in seconds). The corrected Q–T interval is abnormal if it is greater than 0.44 sec at most ages; some normal newborns may have normal Q–Tc of 0.45 sec.

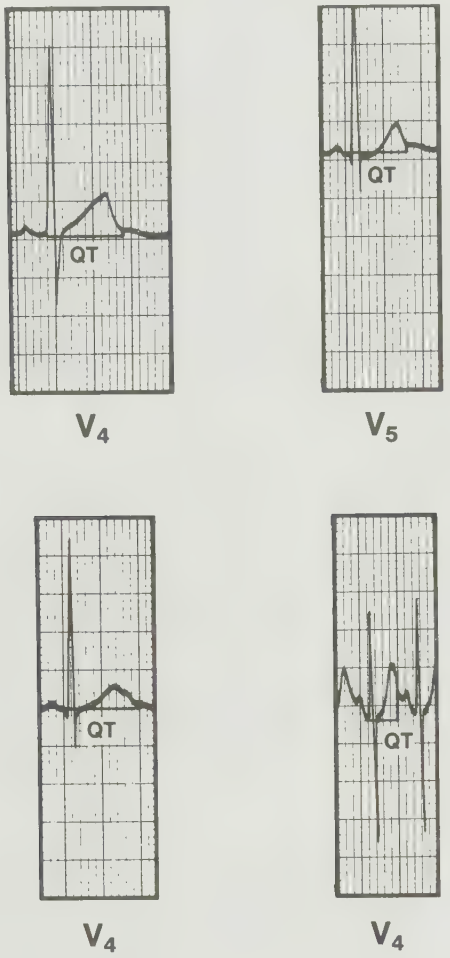


Fig. 45–19. Measurement of the Q–T interval. (A) With a notched T wave followed by a U wave, the downslope of the T wave is extrapolated to the base line. (B) With a notch less than 50% of the peak of the T wave, the early segment is extrapolated to the base line. (C) With a notch greater than 50% of the peak of the T wave, the second portion of the wave is extrapolated to the base line. (D) With superimposed P waves, the downslope of the T wave is extrapolated to the base line.

Q–OT Interval

The interval from the onset of the QRS complex to the onset of the T wave is the Q–OT interval. This interval may be corrected for heart rate in a similar way to the Q–T interval thus determining the Q–OTc interval. In hypocalcemia, the entire T wave is shifted later in the cardiac cycle (due to a prolonged ST segment) and the Q–QTc interval provides a measure of this prolongation (Fig. 45–20). In premature infants, the normal corrected Q–OTc is 0.20 sec or less and in full-term infants, it is 0.19 sec or less.[16]

MALPOSITION OF THE HEART

Atrial Situs

In the majority of cases, the atrial situs may be determined from the electrocardiogram. In situs solitus of the atria and viscera, the P-wave mean vector in the frontal plane is approximately +60°, pointing away from its site of origin in the high right atrium, or away from the right shoulder. This results in a positive P wave in leads I and aVF (Fig. 45–21). In atrial situs inversus, a normal sinus impulse still originates high in the anatomic right atrium but since the anatomic right atrium is on the patient's left, the origin of the P wave appears to be from the left shoulder and the P-wave mean vector in the frontal plane, pointing away from the site of origin, is +120°, resulting in a P wave that is negative in lead I and positive in aVF. The P-wave mean vector in the horizontal plane is generally not helpful because activation proceeds posteroanteriorly in this plane.

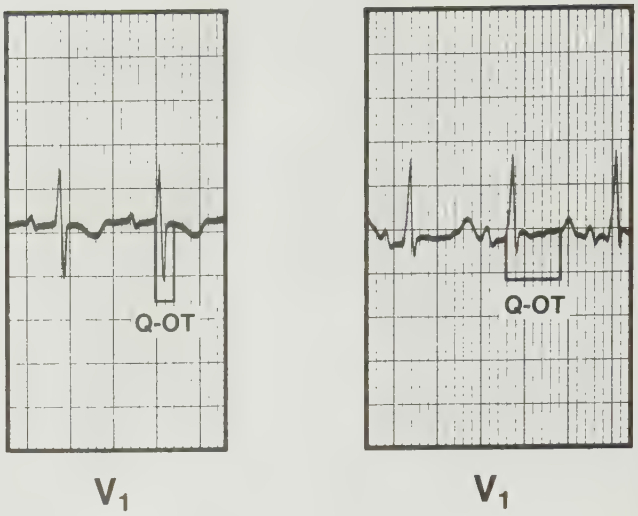


Fig. 45–20. Q–OT interval. (A) Q–OT interval in a normal newborn infant. The Q–OT interval is 0.10 sec and the P–R interval is 0.45 sec. Therefore the Q–OTc interval is 0.15 sec. A normal Q–OT interval is 0.20 sec or less. (B) Q–OT interval in an infant with hypocalcemia. The Q–OT interval is 0.27 sec and the P–R interval is 0.47 sec. The Q–OTc interval of 0.39 sec is prolonged.

It may be impossible to determine atrial situs in the presence of an ectopic atrial rhythm.[17] However, in patients with normal situs and left atrial ectopic rhythm, despite the negative P wave in lead I, there may be a dome-and-dart P wave in lead V_1 (see Fig. 45–21), indicating that the anatomic left atrium is activated before the anatomic right atrium.[18] In the rare case of a patient with atrial situs inversus and an ectopic rhythm originating from the right-sided anatomic left atrium, this patient would have a normal frontal plane P-wave axis (+60°) but with a dome-and-dart configuration in lead V_1 (see Fig. 45–21).

In cases of situs ambiguus associated with splenic malformations, the P waves may be characteristic. In asplenia, there may be two anatomic right atria, one on either side, and there may be two sinus nodes.[19] In such cases, competition between the sinus nodes may occur with two P waves (one positive in lead I and one negative in lead I), each having a slightly different rate. In polysplenia, there may be absence of any sinus node and the pacemaker characteristically is located in the low atrium, giving a frontal plane P-wave mean vector that is directly superior (−90°).

Ventricular Position

Since atrial situs is independent of ventricular position, the P waves and QRS complexes should be interpreted independently

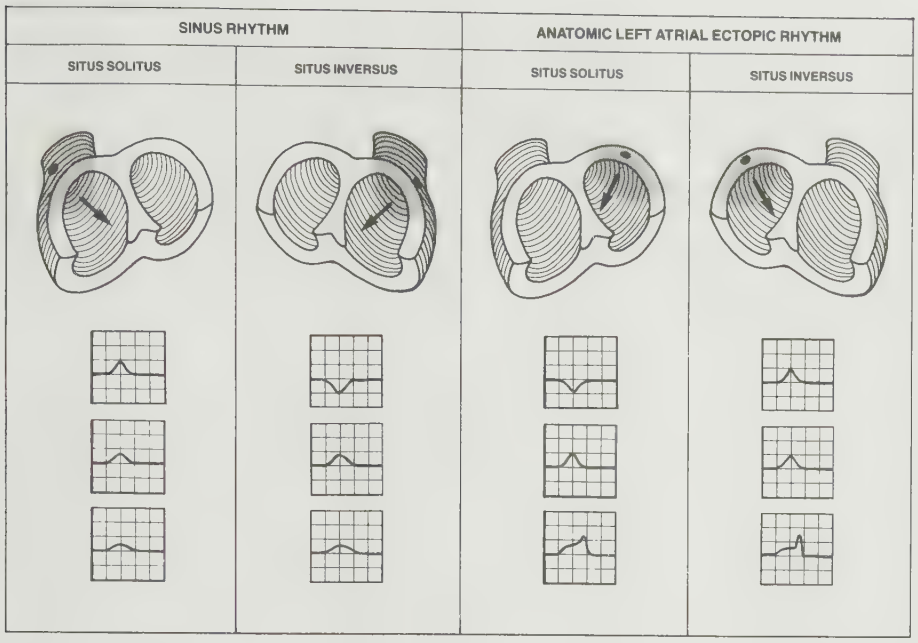


Fig. 45–21. P-wave morphology in sinus rhythm and anatomic left atrial ectopic rhythm with different atrial position. In sinus rhythm, the P wave is positive in lead I with situs solitus and negative in lead I with situs inversus. If the anatomic right atrium is depolarized before the anatomic left atrium, there is a normal P wave in lead V_1. If the anatomic left atrium is activated before the anatomic right atrium, a "dome-and-dart" P wave is found in lead V_1. Therefore in situs solitus with anatomic left atrial ectopic rhythm, there is a negative P wave in lead I and a dome-and-dart P wave in lead V_1. With atrial situs inversus and anatomic left atrial ectopic rhythm, there is a positive P wave in lead I and a dome-and-dart P wave in lead V_1.

(i.e., a negative P wave in lead I suggests atrial situs inversus but not necessarily dextrocardia). There are four major electrocardiographic patterns that describe ventricular position: normal, mirror-image dextrocardia, dextrorotation, and ventricular inversion (Fig. 45–22). In the normally positioned heart, the maximal biphasic QRS voltage in the chest leads (transition) is at the left midclavicular line at lead V_3 or V_4; in the frontal plane, the initial forces are directed superiorly and to the right (Q wave or R wave in leads I, aVF, and V_6), the major forces are directed inferiorly and to the left (tall R wave in leads I, aVF, and V_6), and the terminal forces are directed superiorly and to the left (small S wave in lead aVF, R wave in leads I and V_6) (Fig. 45–23).

Mirror-Image Dextrocardia

"Dextrocardia" implies only that the ventricular mass is in the right chest. In mirror-image dextrocardia, there is a reversal of anatomic left–right relation, but with anteroposterior relation maintained, i.e., the anatomic right ventricle is to the left and anterior. Whenever the ventricles are in the right chest, the maximal biphasic voltage is recorded in one of the right chest leads. If the total voltage (top of the R wave to bottom of the S wave) in lead V_3R or V_4R is larger than the total voltage in lead V_3 or V_4, the patient has dextrocardia. In mirror-image dextrocardia, if all the right chest leads are recorded (V_1 and V_3R to V_7R) the QRS morphologies in these leads should be the same as those found recording the left chest leads in a normally situated heart. In the frontal plane, in a patient with mirror-image dextrocardia, the initial forces are directed superiorly and to the left (initial deep Q wave in leads I, aVF, and V_6); the major forces are directed inferiorly and to the right (small R, deep S, or QS, in leads I and V_6, tall R in aVF) and the terminal forces are directed superiorly and to the right (S wave in leads I, aVF, and V_6) (see Fig. 45–23).

In summary, mirror-image dextrocardia should be suspected 1) if the magnitude of the total QRS deflection is greater in lead V_3R or V_4R than in lead V_3 or V_4; 2) if lead I has a deep Q wave and a small R wave; or 3) if in leads V_3 to V_7, the QRS complexes

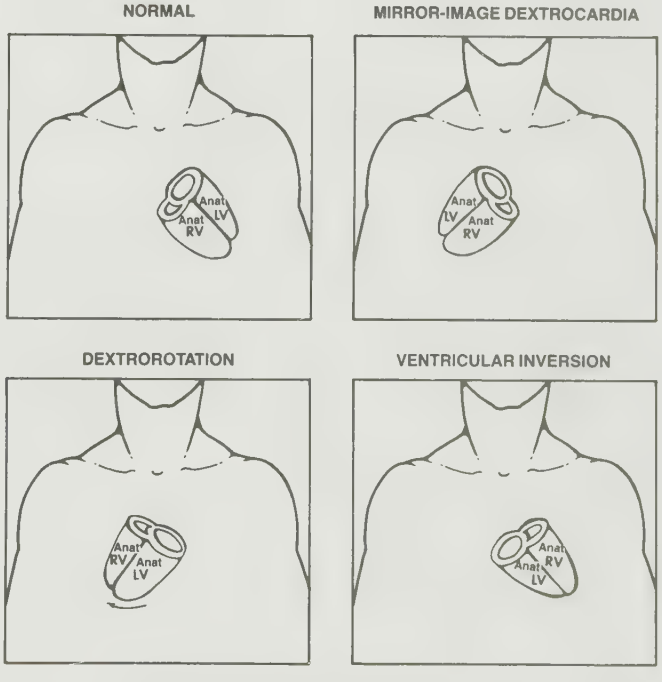


Fig. 45–22. Ventricular position. In the normal heart, the anatomic right ventricle is to the right of and anterior to the anatomic left ventricle. The cardiac mass is in the left chest. In mirror-image dextrocardia, the anatomic right ventricle is to the left of and anterior to the anatomic left ventricle. The ventricular mass is in the right chest. In dextrorotation, the anatomic right ventricle is to the right of and posterior to the anatomic left ventricle. The ventricular mass is in the right chest to a varying degree. In ventricular inversion, the anatomic right ventricle is to the left of and usually side by side of the anatomic left ventricle. In ventricular inversion without dextrocardia, the ventricular mass is in the left chest.

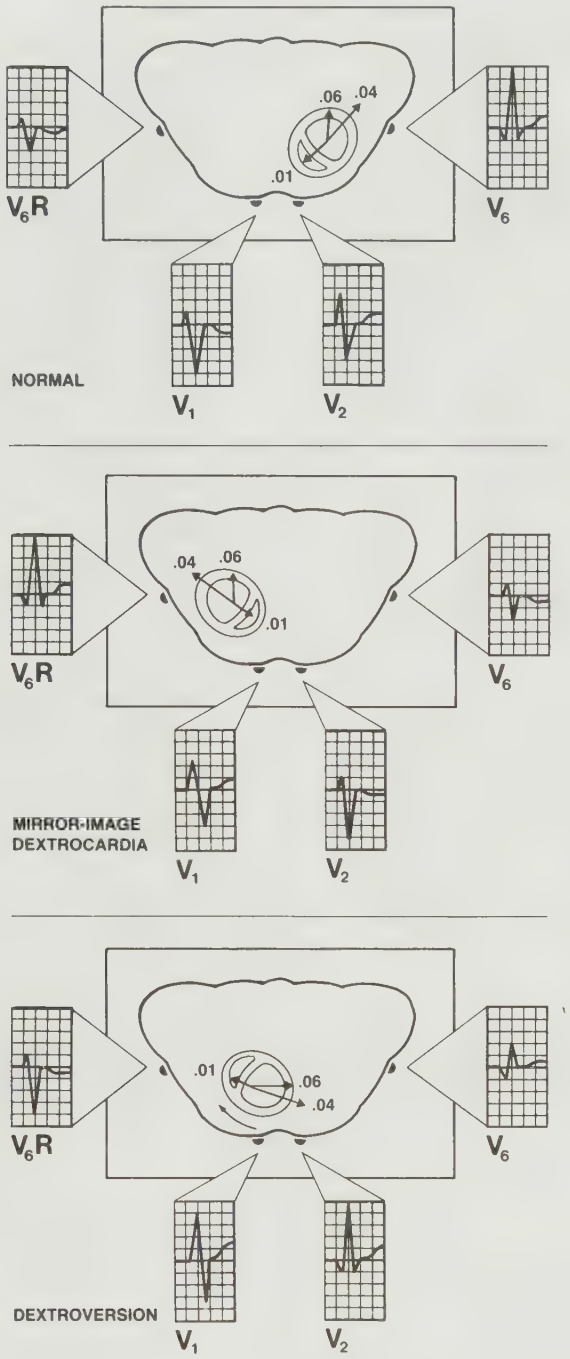


Fig. 45–23. Horizontal-plane vectors in different cardiac positions. In the normal, the middle (0.04 sec) vector points left and posterior. In miror-image dextrocardia, the middle (0.04 sec) vector points to the right and posterior and in dextroversion, the middle (0.04 sec) vector points left and slightly anterior.

become progressively smaller with a small R, deep S, or QS, configuration.[6]

In assessing ventricular hypertrophy in mirror-image dextrocardia, the same criteria can be applied as with normally situated ventricles except that instead of lead V_6, lead V_6R should be substituted and instead of lead V_1, lead V_2 should be substituted (Fig. 45–24). Therefore, even in the absence of a tracing with all the right chest leads, ventricular hypertrophy can be assessed by interpreting lead V_2 as if it were lead V_1 in a normally situated heart.

Dextrorotation

In dextrorotation, the anatomic relations between the ventricles are preserved (i.e., the right ventricle is on the right and the left ventricle is on the left), but the heart is shifted to a varying degree into the right chest. This shift is usually accompanied by a counterclockwise rotation of the heart (viewed from the apex) such that the left ventricle is anterior to the right ventricle (see Fig. 45–22). Since the amount of rightward shift is variable, the classic signs of dextrocardia with greater voltage in the right chest leads than the left, may be missing. In the frontal plane, the direction of the initial, major and terminal deflection may be similar to normally situated ventricles. The mean frontal-plane QRS vector is inferior and slightly to the left or right. The major effect is on the precordial leads, where the transition is found in leads more to the right than normal, i.e., in lead V_3R or V_4R (see Fig. 45–23). The far right chest leads (e.g., lead V_6R) appear similar to the normal V_1 and the anterior leads (V_3) appear similar to the normal V_6. This can be suspected in a routine electrocardiogram when the anterior chest leads (V_2 to V_4) have small Q waves and tall R waves (similar to the normal V_6) and the transition is just beginning in lead V_1 or V_3R.

Ventricular hypertrophy is less accurately assessed in dextrorotation since the degree of rotation is unknown; but similar criteria to those used for mirror-image dextrocardia may be applied with caution.

Ventricular Inversion

One other condition in which the ventricles are malposed is ventricular inversion. In ventricular inversion with otherwise normal cardiac position (atrial situs solitus and levocardia, i.e., with the ventricles in the left chest), the ventricular septum is oriented straight anteroposteriorly and parallel to the diaphragm with the ventricles side by side and the anatomic right ventricle to the left of the anatomic left ventricle (see Fig. 45–22). Since the anatomic left bundle branch is on the right, this results in reversed septal depolarization with a Q wave in lead V_1, and an absent Q wave in lead V_6 (Fig. 45–25). The other characteristics of ventricular inversion and an otherwise normal heart are left-axis deviation in the frontal plane and atrioventricular block (first-, second-, or third-degree). Usually ventricular inversion is accompanied by additional cardiac malformations and the electrocardiogram may deflect these additional anatomic abnormalities.

Pectus Excavatum and Straight Back Syndrome

In both of these conditions, the mediastinum is shortened in the anteroposterior dimension, causing the heart to shift to the left and rotate clockwise as viewed from the apex. This brings the right atrium more anterior relative to the left atrium and so the

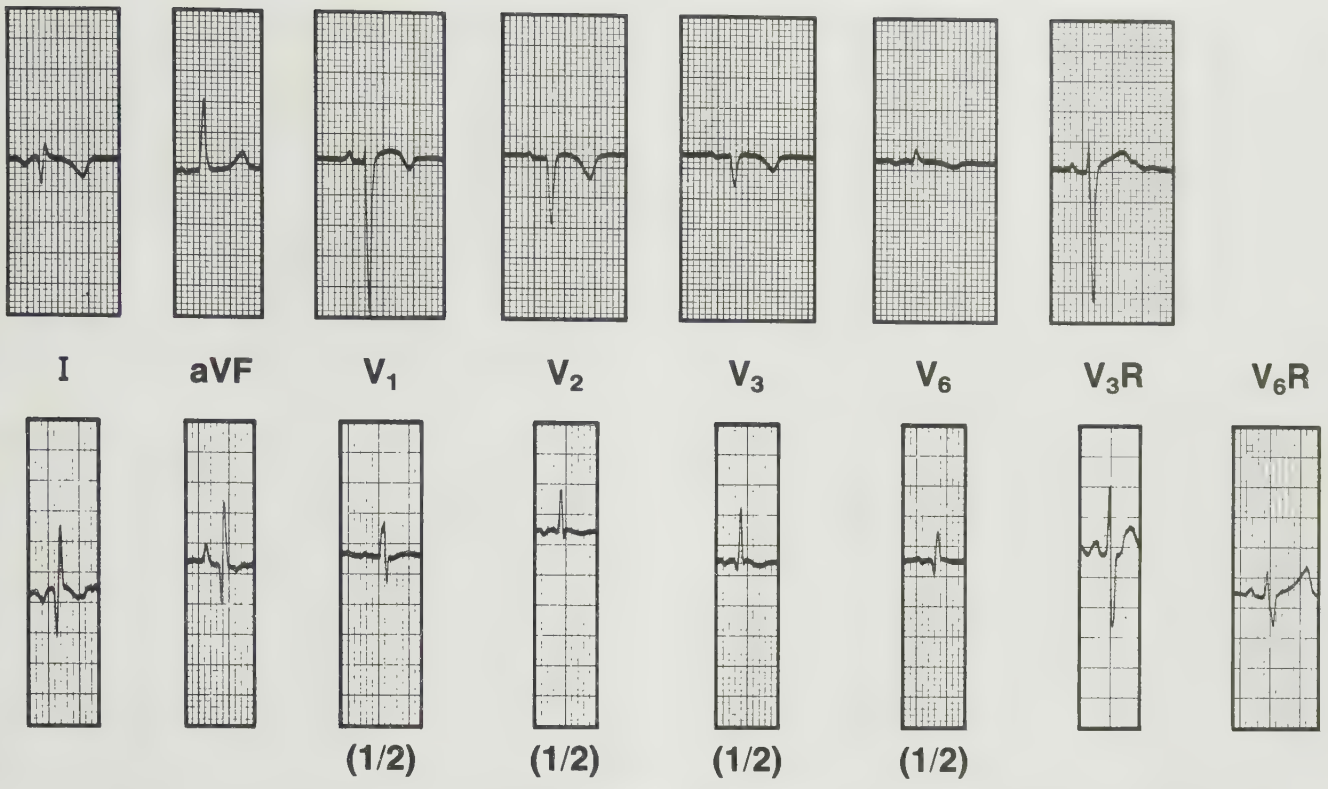


Fig. 45--24. Top tracing: 7-yr-old with dextrocardia and situs inversus with an otherwise normal heart. Bottom tracing: 6-mo-old with dextrocardia, situs inversus, and anterior ventricular hypertrophy. There is a QR pattern in lead V_2 and a deep S wave in lead V_6R.

mean vector of atrial depolarization is oriented straight posteriorly. Therefore, in lead V_1, the P wave may be entirely negative.[8]

Clockwise rotation moves the left side of the heart posteriorly and superiorly causing some patients to have left-axis deviation of the QRS in the frontal plane.[20] The right side of the heart is rotated anteriorly and inferiorly such that the vector of depolarization in the pulmonary outflow tract is shifted from its normal superior and rightward position to a straight anterior position. This is responsible for the normal duration RSR′ pattern in lead V_1 often found in these patients.[21] The transition is shifted to the left and there may be a persistent S wave in lead V_7. Abnormally deep QS waves followed by an R wave of normal duration and inverted T wave in the anterior and midprecordial leads may occur rather than the RSR′ and simulate anterior myocardial infarction. These changes can be explained by the clockwise rotation shifting the major QRS forces even more posteriorly, causing the deep QS and concordantly the inverted T wave. The terminal R wave has the same genesis as the R′ that may be found in this condition: normal terminal depolarization of the right ventricular outflow tract.

Pneumonectomy

The chronic electrocardiographic changes following pneumonectomy result from shift and rotation of the heart. Following a right pneumonectomy, the findings are similar to those of congenital dextrorotation with the transition moved to the right in the chest leads.[22] In over 90% of children after a left pneumonectomy, the heart was rotated clockwise with findings similar to those reported in pectus excavatum.

Pneumothorax and Pneumomediastinum

Since air is a poor conductor of electrical activity, if there is air between the heart on the recording electrode, the voltage of the P, QRS, and T waves will be decreased. In pneumomediastinum, the voltage may be decreased in all leads. In pneumothorax, the voltage may be decreased only in certain leads corresponding to the location of the air. Depending upon the amount of air, a pneumothorax may cause shift or rotation of the heart similar to that found following pneumonectomy on the opposite side. Finally, depending upon the amount of hemodynamic compromise caused by the condition, nonspecific ST- and T-wave changes, as well as arrhythmias, may occur. In pneumothorax, if the patient is placed in a sitting position, the electrocardiogram may normalize as the air moves superiorly away from the heart.

Kyphoscoliosis

There may be virtually any positional abnormality with kyphoscoliosis.[8] In severe cases, both rotation and shift occur thus making it even more difficult to interpret the electrocardiogram. Since respiratory insufficiency and cor pulmonale may occur in these children and cause right atrial enlargement, right-axis deviation, and right ventricular hypertrophy, an electrocardiographic diagnosis may be helpful in the treatment of the patient. As a general rule, a P-wave amplitude of more than 2.5 mm in any lead constitutes right atrial enlargement. Right ventricular hypertrophy should be considered if a complex is found in any precordial lead to the right of the transitional leads with a tall R wave and a small S wave, and the height of the R wave is greater than the normal value for age given for lead V_1.

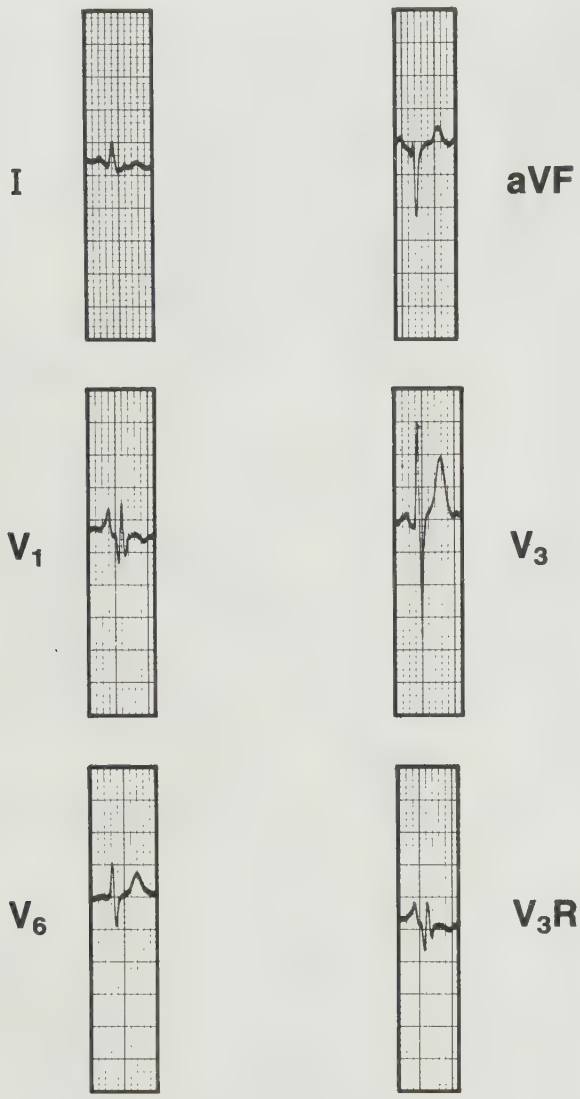


Fig. 45–25. Ventricular inversion. Note the deep Q waves in lead V_1 with a relatively small R wave. There are no Q waves in lead V_6.

CHAMBER ENLARGEMENT AND HYPERTROPHY

The electrocardiogram can be helpful in the diagnosis of enlargement or hypertrophy of the cardiac chambers. While the electrocardiogram correlates with chamber size better in pediatric patients than in adults, there is still only about a 60 to 70% predictive value of the electrocardiogram in children.[23,24] Therefore if either the presence or absence of an abnormality on an electrocardiogram does not agree with the clinical or echocardiographic findings, the electrocardiogram should be viewed critically. In the following discussion, criteria are listed for chamber enlargement or hypertrophy with the most reliable signs presented first.

Right Ventricular Hypertrophy

The electrocardiogram can provide important data on right ventricular hypertrophy or elevated right ventricular systolic pressure that are not currently available by noninvasive means. The criteria for right ventricular hypertrophy are described below.

QR Pattern in the Right Chest Leads (Fig. 45–26). The Q wave is due to dominant early wave of excitation moving posteriorly. This may be due to the hypertrophied and dilated right side of the septum providing a larger surface area for a normally insignificant posterior vector. In this case, left to right septal activation occurs normally but is overshadowed by a stronger posterior vector. Alternatively, in right ventricular hypertrophy, the inferior wall of the right ventricle directly contiguous to the septum may bulge posteriorly and to the left of the septum. Therefore, instead of the earliest activation continuing left to right, the initial septal depolarization may begin normally toward the right for a few milliseconds but then change orientation and move to the left as the parts of the inferior wall of the right ventricle that are situated to the left of the septum depolarize.[25]

The Q wave in the QR pattern of right ventricular hypertrophy is generally only 0.5 to 1 mm deep in infants but may become 3 to 5 mm deep in older children. The QR pattern is reliable and implies a right ventricular systolic pressure of 70 mm Hg or more at any age.[26] A QR pattern may also be seen in ventricular inversion with reversed septal depolarization. In general, in the QR pattern of right ventricular hypertrophy in lead V_1 or V_4R, the R wave is tall (more than 10 mm). In ventricular inversion, the Q wave may be slightly deeper than the usual Q wave seen in right ventricular hypertrophy and the R wave may not be as tall (see Fig. 45–25). This distinction may not be possible in an individual patient. A final cause of a QR pattern in lead V_1 or V_3R is the rare case of an anterior myocardial infarction involving either the right ventricle or the anterior ventricular septum. Before making the diagnosis of a QR pattern, it is important to be certain that the QRS complex does not begin with a tiny R wave, thus making the complex an RSR′ pattern rather than a QR pattern.

T-Wave Changes. Between 1 wk of age and the onset of adolescence, the T waves in the right chest leads should be negative. In mildly increased right ventricular systolic pressure, the electrocardiogram is normal with a small R wave and a symmetrically inverted T wave in lead V_1 (Fig. 45–27). With increasing severity of pulmonary stenosis, usually before the R wave height is abnormal, the T wave becomes isoelectric or upright (see Fig.

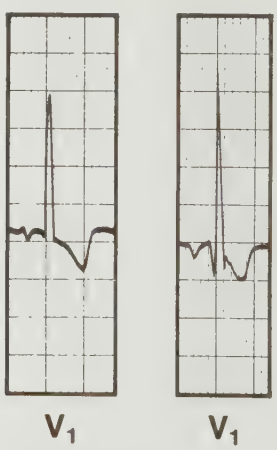


Fig. 45–26. Left: Typical QR pattern in lead V_1 with a small Q wave. This is from a 9-mo-old patient with unoperated transposition of the great arteries. Right: Deep Q wave with a tall R wave and ST depression in a 4-yr-old after Mustard operation for transposition of the great arteries.

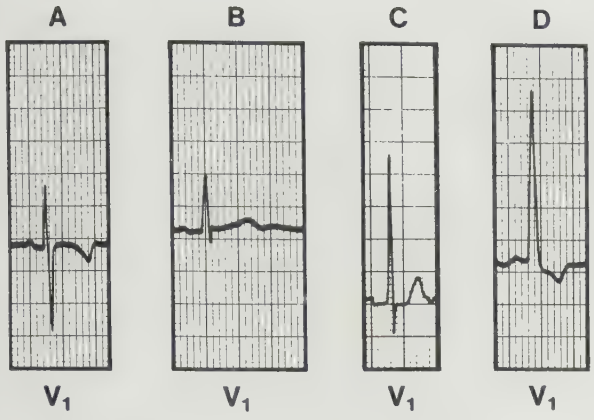


Fig. 45–27. Progression of T-wave changes in lead V_1 in right ventricular hypertrophy. (A) Normal T wave in a 4-year-old child. (B) Upright T wave in a 7-yr-old child with mild pulmonary stenosis. The R wave is 9 mm tall. (C) Tall R wave with upright T wave in a 2-year-old with severe pulmonary stenosis. (D) Tall R wave with asymmetrically inverted T wave ("right ventricular strain") in a 3-yr-old patient with critical pulmonary stenosis.

45–27). The upright T wave is due to elevated right ventricular systolic pressure and not necessarily to right ventricular hypertrophy, since in a patient with increased right ventricular systolic pressure due to upper airway obstruction and hypoxia, the upright T waves may invert immediately with intubation and ventilation. In general, if the height of the R wave in lead V_1 is less than 10 mm, an inverted T wave is associated with less severe disease than an isoelectric or upright T wave (see Fig. 45–27). When the R-wave height increases above 10 mm, the upright T wave may become asymmetrically inverted with a concave upward terminal portion (see Fig. 45–27). Therefore the progression and severity is as follows: normal R with symmetrically inverted T; normal or slightly increased R with upright T; tall R with upright T; and tall R with asymmetrically inverted T. The asymmetrically inverted T wave in lead V_1 is called the "right ventricular strain" pattern and may be associated with ST depression in the same lead. This is thought to be a primary T-wave change due to the reversed direction of repolarization, which occurs from endocardium to epicardium in hypertrophy.[4] The right ventricular strain pattern generally indicates a right ventricular systolic pressure equal to or greater than systemic pressure.[6,26] The deeply asymmetrically inverted T waves in the right ventricular strain pattern may extend as far to the left as lead V_4 and, rarely, V_5 but usually not to V_6.[25] Conversely, the T-wave inversion found in leads V_5 and V_6 indicating "left ventricular strain" may cause reciprocally upright T waves in the right chest leads. Therefore, before the diagnosis of right ventricular hypertrophy is made on the basis of an upright T wave in lead V_1, leads V_5 and V_6 should be examined for left ventricular strain.

One other T-wave change of severe right ventricular hypertrophy is T-wave inversion in lead aVF.[26] This is a nonspecific sign, since it may also be indicative of left ventricular strain or another condition (see section on "Ischemia"). But in the presence of other signs of right ventricular hypertrophy, T-wave inversion in lead aVF indicates severe right ventricular hypertrophy.

R-Wave Amplitude in Lead V_1. If the amplitude of the R wave in lead V_1 exceeds the ninety-eighth percentile for age (see Table 45–1) right ventricular hypertrophy is suspected. This sign is more specific but less sensitive than others; i.e., there may be children with right ventricular hypertrophy with a normal R wave in lead V_1.[8] The magnitude of the R wave in lead V_1 is directly proportional to the right ventricular systolic pressure. Two correlative formulas have been devised from children with pulmonary stenosis. Right ventricular systolic pressure equals three times the R wave in V_1 plus 47, or right ventricular systolic pressure equals five times the R wave in V_1.[25,26] If the R wave in V_1 is 20 mm Hg or more at any age, the right ventricular systolic pressure is equal to or more than systemic pressure.

One other reason for an abnormally tall R wave in lead V_1 in a patient without right ventricular hypertrophy is ventricular septal hypertrophy. This may cause deep Q waves in leads V_5 and V_6, with reciprocally tall R waves in lead V_1. Since septal depolarization is completed relatively early in the QRS complex, the tall R wave in lead V_1 due to septal hypertrophy is "narrow" and usually lasts 0.03 sec or less. Conversely, in right ventricular hypertrophy, ventricular activation is slightly prolonged and the R wave of right ventricular hypertrophy in lead V_1 generally lasts 0.04 sec or longer.[8] Finally, in patients with muscular dystrophy, a similar pattern of a tall narrow R wave in V_1 may occur with Q waves in the left chest leads. This is thought to be due to posterobasal left ventricular fibrosis.

S-Wave Amplitude in Lead V_6. If the depth of the S wave in lead V_6 exceeds the ninety-eighth percentile for age (see Table 45–1), right ventricular hypertrophy is suspected. This is more sensitive and less specific than other signs; i.e., a deep S wave in lead V_6 may be associated with conditions other than right ventricular hypertrophy. One of these is left ventricular hypertrophy localized to the superior septum. This part of the left ventricle is the last to be activated, and since it is usually in the anterior part of the left ventricle, this may cause a delayed vector directed anteriorly, causing an S wave in lead V_6 or even a normal duration RSR′ in lead V_1. This has been termed the "incomplete right bundle branch block of coarctation of the aorta or aortic stenosis."[25] One other cause of a deep S wave in lead V_6 is left anterior hemiblock caused by delayed activation of the anterior left ventricle (see section on "Interventricular Conduction Disturbance").

R/S Ratio in Lead V_1. This ratio suffers the inaccuracies of each of the single measurements. Nonetheless, an abnormally large R/S ratio does correlate with right ventricular hypertrophy (see Table 45–1), and it is a stronger sign for right ventricular hypertrophy in the presence of a deep S wave in lead V_6.

RSR′ in Lead V_1. In more than 90% of children with a secundum atrial septal defect, there is a normal duration RSR′ pattern in lead V_1. This correlates well with the mild right ventricular hypertrophy found in these children.[6] Thus the RSR′ pattern is quite sensitive for mild right ventricular hypertrophy but also quite nonspecific, since it may be found in normal children and those with incomplete right bundle branch block (see the sections on "The Normal Electrocardiogram" and "Interventricular Conduction Disturbance"). In right ventricular hypertrophy, the S wave tends to be smaller and the R′ wave larger than in normal children. With a QRS complex of normal duration, right ventricular hypertrophy is usually the cause of an R′ wave greater than 15 mm in an infant under 1 year of age, or an R′ greater than 10 mm over 1 year (Fig. 45–28). If the R′ is small with a normal duration RSR′ complex, the diagnosis could be normal, incomplete right bundle branch

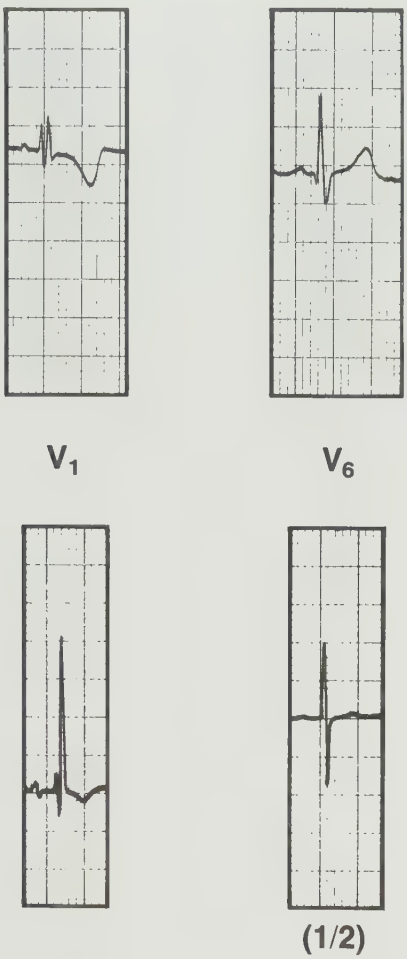


Fig. 45–28. The RSR′. Top tracings: QRS complex of normal duration with RSR′ pattern in V_1 in a 6-yr-old child. The R′ is not tall. No specific diagnosis can be applied. Bottom tracings: QRS complex of normal duration with an RSR′ pattern in lead V_1. The R′ wave is tall. This is a 6-mo-old child with right ventricular hypertrophy.

block pattern or right ventricular hypertrophy and we would prefer the description "RSR′ pattern in right chest leads" rather than attempting to make a specific diagnosis.

Right-Axis Deviation. Over the age of 3 mo, right-axis deviation correlates with right ventricular hypertrophy.[27] In adults, one of the common causes of right-axis deviation is left posterior hemiblock (see section on "Interventricular Conduction Disturbance"). Left posterior hemiblock is rare in children, so right ventricular hypertrophy is by far the leading cause of right-axis deviation in children. Nonetheless, right-axis deviation should be considered as supporting evidence, and the electrocardiogram should meet one of the other criteria for right ventricular hypertrophy. The diagnosis of right-axis deviation may be stronger supporting evidence for right ventricular hypertrophy in the patient with an RSR′ pattern in lead V_1.[28]

Left Ventricular Hypertrophy

Recent echocardiographic and autopsy studies have shown that the electrocardiographic diagnosis of left ventricular hypertrophy is accurate only about 50% of the time. The more of the criteria described below that are met by an electrocardiogram, the more certain is the diagnosis of left ventricular hypertrophy.[4]

T-Wave Changes. The T waves are normally upright in leads V_5 and V_6 after 48 hr of age. The most reliable sign of left ventricular hypertrophy is asymmetric T-wave inversion with an upward convexity in the terminal portion of the T wave in leads V_5 or V_6—the so-called left ventricular strain pattern (Fig. 45–29). This may coexist with ST depression in the same leads. These changes become more prominent with increasing left ventricular to aortic gradient in aortic stenosis in children. In all children with a gradient less than 50 mm Hg, the T waves in lead V_6 were upright, whereas 50% of those with gradients of 80 mm Hg or more had inverted T waves in lead V_6. The T waves in lead aVF also became inverted with increasing gradient in aortic stenosis, but the findings in leads V_5 and V_6 were more reliable.[24]

The ST–T-wave changes of left ventricular strain are the opposite of what would be expected in hypertrophy. In mild hypertrophy, the R wave in lead V_6 is increased in amplitude and the positive T waves are also increased in amplitude. In severe left ventricular hypertrophy, there is a variable amount of conduction delay and endocardial repolarization begins before epicardial depolarization has ended, causing T-wave inversion and ST-segment depression (see Fig. 45–29). Left ventricular strain is therefore a primary change unrelated to the height of the R wave.[4]

T-wave inversion in the inferior and lateral leads is found in conditions other than severe left ventricular hypertrophy (see section on "Ischemia"). But if no other cause is found for the T-wave inversion, even in the absence of other criteria, the diagnosis of severe left ventricular hypertrophy should be suspected on the basis of the T waves.

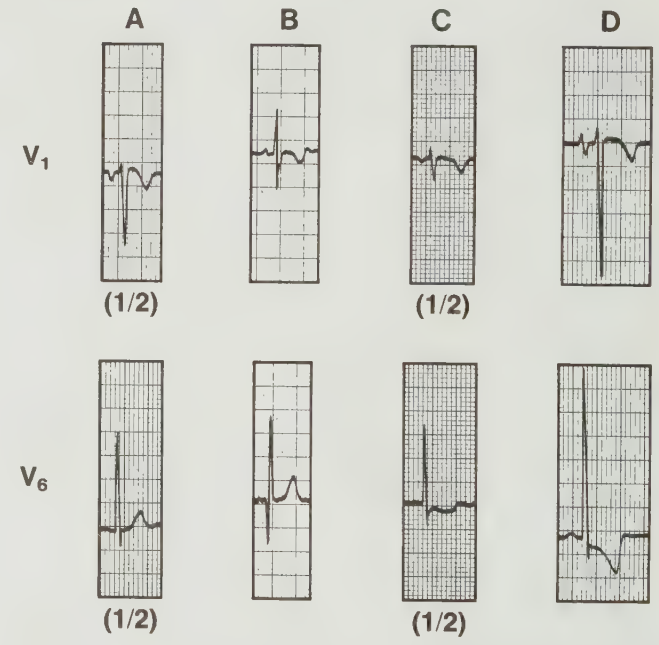


Fig. 45–29. Left ventricular hypertrophy. (A) Voltage criteria with deep S wave in lead V_1 and tall R wave in lead V_6. (B) Deep Q waves in lead V_6. (C) Absent Q wave in lead V_6. (D) T-wave inversion in lead V_6 with ST depression ("left ventricular strain").

R-Wave Amplitude in Lead V_6 or S-Wave Amplitude in Lead V_1. An R wave in lead V_6 or an S wave in lead V_1 that is greater than the ninety-eighth percentile for age (see Table 45–1) should be designated as "left ventricular hypertrophy by voltage criteria" (see Fig. 45–29). Morganroth et al.[29] reported on 11 teenagers with either an abnormally deep S wave in lead V_1 or an abnormally tall R wave in lead V_6, all of whom had a normal echocardiogram and no other evidence of cardiac disease. All of these children had normal T waves. Therefore an individual adolescent may have prominent voltage without an increased left ventricular mass. In the absence of T-wave changes, the diagnosis of left ventricular hypertrophy based entirely on voltage criteria must be viewed critically.

Amplitude of the R Wave in Lead V_6 plus the Amplitude of the S Wave in Lead V_1. This measurement suffers from the same problem as the individual measurements, but does correlate with left ventricular hypertrophy. This should also be considered as "left ventricular hypertrophy by voltage criteria" if greater than the ninety-eighth percentile for age (Table 45–1). The R/S ratio in the precordial leads is less helpful in left ventricular hypertrophy than right ventricular hypertrophy.

Q-Wave Abnormalities. The 0.01-sec vector consists of the net result of almost simultaneous activation of the anterior left ventricle, posterior left ventricle, and left side of the septum. Therefore if any of these areas is hypertrophied the normal balance of forces may be upset and the initial portion of the QRS complex may change. The Q waves may vary independently from the R and S waves.

In left ventricular hypertrophy due either to a dilated left ventricle (aortic insufficiency or ventricular septal defect), septal hypertrophy (hypertrophic cardiomyopathy), or mild aortic stenosis, the initial forces may be increased in the right anterior-superior direction causing abnormally deep Q waves in the inferior and lateral leads (leads II, III, aVF, V_5, V_6).[30] The other causes for abnormally deep Q waves are discussed in the section on "Infarction."

In advanced concentric left ventricular hypertrophy with increased thickness of the posterior wall and septum, the QRS vector shifts to the left and posteriorly, causing the initial forces to be directed more to the left. This may cause the absence of a Q wave in lead V_6 (Fig. 45–29C). In children with aortic stenosis, an absent Q wave in lead V_6 was more than twice as common in those with a severe gradient than in those with a gradient less than 50 mm Hg.[24] Nonetheless, 53% of those with a gradient of at least 80 mm Hg had a 1- or 2-mm Q wave in lead V_6. The terms "volume overload" and "pressure overload" type of left ventricular hypertrophy have been associated with deep Q waves and absent Q waves, respectively.[30] Since there is so much overlap, I prefer not to use this terminology. Nonetheless, the absence of a Q wave or the presence of an abnormally deep Q wave may be supportive evidence of left ventricular hypertrophy.

Biventricular Hypertrophy

Abnormal Voltage in Both the Right and Left Chest Leads. In the presence of isolated hypertrophy of one ventricle, the forces reflecting the other normal ventricle usually appear diminished on the electrocardogram. For example, in isolated right ventricular hypertrophy with a tall R wave in lead V_1 and a deep S wave in lead V_6, the forces reflecting the left ventricle (S wave in lead V_1 or R wave in lead V_6) are usually diminished because of the dominance of the other ventricle. Thus biventricular hypertrophy can be diagnosed if in the presence of voltage criteria for hypertrophy of one ventricle the other ventricle generates at least normal forces. Therefore, one criterion for biventricular hypertrophy is right ventricular hypertrophy (abnormally tall R wave in lead V_1 or deep S wave in V_6) and either an S wave in lead V_1 or an R wave in lead V_6 exceeding the mean for age. (This criterion should not be applied in the same lead [i.e., if the diagnosis of right ventricular hypertrophy is made on the basis of a tall R wave in V_1, then biventricular hypertrophy must be based upon an additional tall R wave in V_6].) Another criterion is left ventricular hypertrophy (abnormally tall R wave in lead V_6 or deep S wave in lead V_1) and either an S wave in lead V_6 or an R wave in lead V_1 exceeding the mean for age (Figs. 45–30A and 45–30B). The same rule about two separate leads applies in left ventricular hypertrophy as was explained for right ventricular hypertrophy. Biventricular hypertrophy should not be diagnosed based on Q-wave or T-wave morphology.

Abnormal Voltage in the Midprecordial Leads. Prominent midprecordial voltage is a sign of biventricular hypertrophy. Katz and Wachtel originally described large biphasic QRS complexes in the limb leads of patients with congenital heart disease.[31] The Katz–Wachtel criterion has become broadened to refer to increased midprecordial voltage in patients with biventricular hypertrophy (Fig. 45–30C). In lead V_4, the voltage from the top of the R wave to the bottom of the S wave varies with age (Table 45–1). Biventricular hypertrophy can be diagnosed if the R wave plus the S wave exceeds the ninety-eighth percentile. The Katz–Wachtel criterion of increased midprecordial voltage may be inaccurate because of proximity effects enlarging the midprecordial QRS voltage or cancellation effects reducing the voltage. Usually, if any equiphasic complex has a total R and S more than 60 mm, the patient has biventricular hypertrophy.

Right Atrial Enlargement

Right atrial depolarization is responsible for the early part of the P wave and therefore when right atrial enlargement occurs, this is manifest in the first 0.04 to 0.06 sec of the P wave. The criteria described below may be used in diagnosis.

Increased Amplitude of the P Wave. The right atrium enlarges anteriorly and inferiorly, causing an enlarged P wave of normal duration. The increased early vector causes the P wave to appear peaked. If the P wave in any lead is greater than 2.5 mm in amplitude at any age, right atrial enlargement is diagnosed (Fig. 45–31A).[25,31] The right atrium may occasionally enlarge and wrap around the superior vena cava and inferior vena cava posteriorly as well as anteriorly. In this case, there is an early negative deflection in the first 0.04 to 0.06 sec, which is usually pointed (Fig. 45–31B). This negative deflection, by itself, is not a criterion for right atrial enlargement but needs to be distinguished from the more rounded late terminal negative deflection that is a criterion of left atrial enlargement. If the mean vector of the P wave is such that atrial depolarization is thought to originate from an area other than the sinus node, the electrocardiogram should not be interpreted as indicating atrial enlargement.

The electrocardiographic criteria of right atrial enlargement are related both to high right atrial pressure and high right atrial volume in children.[33] The presence of these changes immediately after an episode of supraventricular tachycardia or pulmonary embolism and their absence after several hours have elapsed implies that

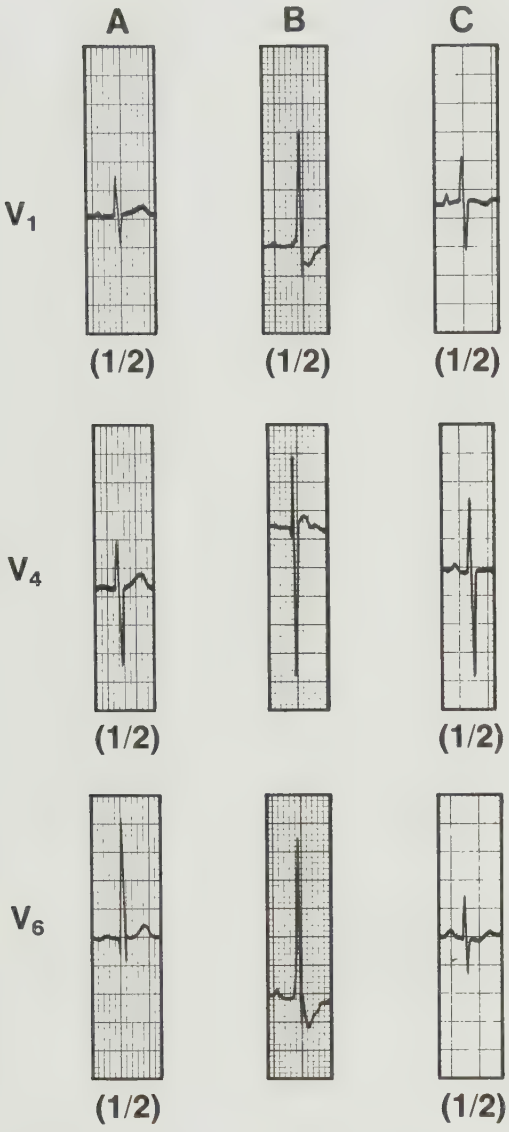


Fig. 45–30. Biventricular hypertrophy. (A) The wave in lead V_6 is 42 mm high. This meets the criterion for left ventricular hypertrophy. The R wave in lead V_1 is 15 mm high. This exceeds the mean voltage for the R wave in lead V_1 for this 1½ year old child, and therefore the diagnosis of biventricular hypertrophy is made. (B) The R wave in lead V_1 is 40 mm high. This meets the voltage criteria for right ventricular hypertrophy. The R wave in lead V_6 is 12 mm high. This exceeds the mean for the R wave in lead V_6 at 1 wk of age and so the diagnosis of biventricular hypertrophy is made. (C) The voltage in leads V_1 and V_6 are not distinctly abnormal for a 1-wk-old baby, however, the voltage in lead V_4 constitutes abnormally prominent midprecordial voltage, and the diagnosis of biventricular hypertrophy is made on this basis. This is the "Katz–Wachtel" criterion.

Fig. 45–31. Right atrial enlargement. Left: tall peaked P wave. Right: early (first 0.04 sec) pointed, negative deflection in lead V_1.

hemodynamics rather than hypertrophy are related to these changes.

Left Atrial Enlargement

Left atrial depolarization is responsible for the terminal portion of the T wave and therefore when left atrial enlargement occurs, this is manifest in the latter part of the P wave. The criteria described below may be used in diagnosis.

Increased Terminal Posterior Forces. The most reliable indicator of left atrial enlargement is a late negative deflection in lead V_1. This deflection begins later than 0.04 sec after the onset of the P wave. In children and adults, if the terminal deflection in lead V_1 is greater than 1 mm deep and greater than 0.04 sec in duration, this indicates left atrial enlargement (Fig. 45–32A).[34] As the left atrial enlargement gets more severe, the depth and duration of the terminal segment increase such that in the most severe left atrial enlargement in children, the mean depth of the P terminal segment in lead V_1 was 2.8 mm and the duration 0.08 sec.[35]

Increased terminal posterior forces are related more to left atrial volume than to pressure. As with the changes in right atrial en-

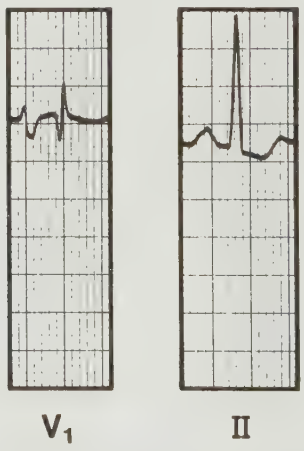


Fig. 45–32. Left atrial enlargement. Left: increased terminal negative deflection. The terminal portion of the P wave is 2.5 mm deep and 0.06 sec wide. Right: increased P-wave duration.

largement, the P waves may become abnormal with an abrupt increase in left atrial volume, such as acute mitral insufficiency, and then may return to normal shortly after the stress is removed, again implying that hypertrophy is not necessary for these changes. In general, the increase in P terminal forces is a specific sign of left atrial enlargement but there may be false negatives.[36] As with right atrial enlargement, if the pacemaker does not originate in the sinus node, left atrial enlargement should not be diagnosed on the basis of the electrocardiogram.

Increased P-Wave Duration. This is a more nonspecific sign either of left atrial enlargement or interatrial conduction delay, which may be found in damage to the atrial myocardium due to myocarditis, fibrosis, or ischemia.[37] An abnormal P-wave duration is defined as longer than 0.09 sec in children younger than age 3 and longer than 0.10 sec in children 3 yr of age or older (Fig. 45–32B). This sign, similar to the increased terminal negative deflection, indicates abnormality when present, but it is not sensitive enough to diagnose most cases of left atrial enlargement in children detected echocardiographically.[36]

Biatrial Enlargement

Since the right and left atria depolarize sequentially, causing different parts of the P wave, and since the signs of enlargement of one atrium do not distort the changes of enlargement in the other atrium, biatrial enlargement is diagnosed when the signs of right atrial enlargement coexist with the signs of left atrial enlargement.

Abnormal Voltage and Duration. If the first 0.04 sec of the P wave are taller than 2.5 mm and the P wave is either prolonged for age or has a late terminal deflection in lead V_1 that is greater than 1 mm deep and 0.04 sec in duration, the diagnosis is biatrial enlargement (Fig. 45–33).

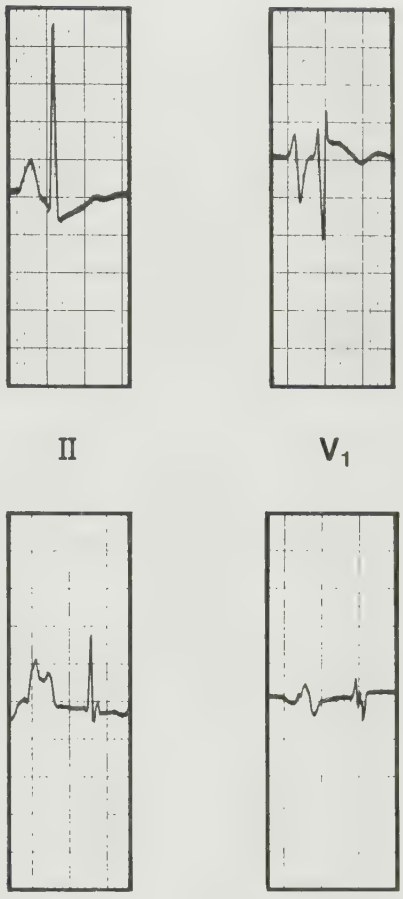


Fig. 45–33. Biatrial enlargement. Top tracings show P waves with increased positive amplitude in lead V_1 as well as a large terminal negative deflection in lead V_1. The P waves also have prolonged duration in addition to increased positive amplitude in lead II. Bottom tracings show P waves that are larger than the QRS complexes. The P wave is the first complex in each lead. The P wave in lead II begins with the sharp positive upstroke and is 6 mm tall. The P wave is 0.16 sec in duration. In lead V_1, there is also a large terminal negative deflection.

INTERVENTRICULAR CONDUCTION DISTURBANCE

Conduction through the ventricles can be disturbed either by delay or by preexcitation resulting in an abnormal sequence of ventricular activation.

Conduction Delay

Right Bundle Branch Block

Right bundle branch block results from delay in right ventricular activation. There is sequential activation of the right ventricle after activation of the left ventricle, rather than simultaneous activation. The conduction delay can occur in the distal His bundle in fibers destined for the right bundle branch, or it may occur in the main portion of the right bundle branch. The pattern is of delayed, slurred activation oriented anteriorly and rightward.[38] It has recently been questioned whether interruption of the peripheral ramifications of the right bundle branch cause the same electrocardiographic pattern.

Complete Right Bundle Branch Block. The QRS pattern is most important for the diagnosis of complete right bundle branch block. There is an initial rapid deflection, followed by a slurred, slower terminal deflection. In lead V_1, the rapid component consists of an R wave and an S wave of varying magnitudes followed by a slurred tall R wave. There may be no S wave, resulting in an RR′ complex (Fig. 45–34). In leads I and V_6, the late slurred terminal deflection causes a broad S wave.

This pattern can be quantified such that the mean duration of the "fast" component (RS of the RSR′) is 0.038 sec in adults, and the time from the end of the fast component to the peak of the R′ is 0.061 sec. Essentially, in lead V_1 the R′ is twice the width of the RS, or in lead V_6, the S wave is twice the width of the R wave. This pattern of discrepancy between the initial and terminal components is a more reliable sign of complete right bundle branch block than the exact duration of the total QRS complex, especially since 0.01 sec or even 0.02 sec may be difficult to measure accurately. The criteria for complete right bundle branch block are QRS duration prolonged for age (greater than 0.09 sec up to the age of 4 yr and over 0.10 sec for 4 yr to 16 yr), normal initial forces (first 0.04 sec), and terminal conduction delay directed anteriorly and to the right.

The axis in complete right bundle branch block considers the frontal plane QRS axis calculated based upon the "fast" initial portion of the complex. Generally, this is the first 0.04 msec; but, the initial rapid portion before the "break" to the terminal slow

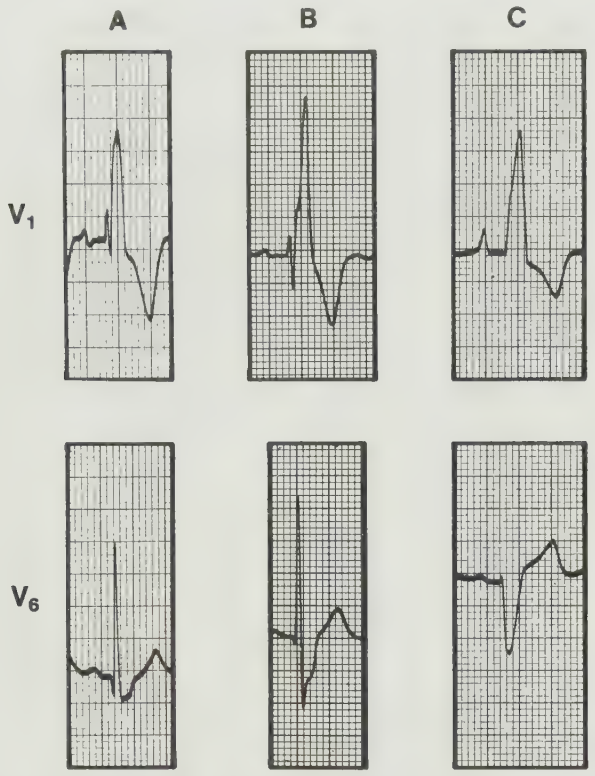


Fig. 45–34. Variations of complete right bundle branch block. In the tracings on the left (A), there is a large R wave and a small S wave; in the tracings in the middle (B), there is a mall R wave and a deeper S wave; and in the tracings on the right (C), there is an R wave without an S wave. The latter part of all three complexes has a slurred component, which is the R′ wave. All three tracings have broad terminal S waves in lead V_6.

portion should be used, regardless of the specific timing. If the frontal-plane axis of the initial "unblocked" portion is between −30° and −90°, this is considered to be left-axis deviation in addition to complete right bundle branch block. This distinction is important in the diagnosis of bifascicular block and will be discussed further in that section.

Attempts have been made to use the axis, as well as the absolute height and proportions of the R, S, and R′ components to diagnose hypertrophy in the presence of complete right bundle branch block. The correlation of these parameters with the ventricular pressure or free wall thickness is insufficient to permit the diagnosis of either right ventricular or left ventricular hypertrophy in the presence of complete right bundle branch block.[39,40] The T-wave changes in complete right bundle branch block are secondary to the abnormal sequence of depolarization.

The most common cause of complete right bundle branch block is surgery involving closure of a ventricular septal defect. Congenital complete right bundle branch block is rare in children, but may occur with autosomal dominant inheritance. Isolated congenital complete right bundle branch block does not appear to progress to further conduction disturbances.[41,42] Complete right bundle branch block may also be a manifestation of inflammation from myocarditis or endocarditis and may progress to complete atrioventricular block.[38] In normal children, functional right bundle branch block or left bundle branch block may occur because of ventricular aberration of a supraventricular rhythm. However, rate-dependent bundle branch block is extremely rare in children and occurred in only 2% of children reported with supraventricular tachycardia.[43]

"Incomplete Right Bundle Branch Block" Pattern. The RSR′ pattern in lead V_1, in which the duration of R′ is approximately equal to the duration of the RS wave (i.e., no terminal conduction delay) has been referred to as the "incomplete right bundle branch block" pattern (Fig. 45–35). The duration of the QRS complex may be normal or slightly prolonged for age (up to 0.09 sec under the age of 4 yr or 0.10 sec from 4 to 16 yr). Approximately 7% of normal children over the age of 6 mo have this pattern.[6] The only major pathologic cause of an incomplete right bundle branch block pattern in childhood is right ventricular diastolic volume overload, and this is found in 93% of children with a secundum atrial septal defect. In children with atrial septal defect, it has been demonstrated that the central right bundle conduction time is normal, therefore implying that the pattern is due to more peripheral factors.[44] This pattern of terminal activation directed anteriorly and rightward is currently explained either by selective hypertrophy of the right ventricular outflow tract or by stretching of the peripheral specialized conduction fibers due to distention of the right ventricular outflow tract.[45] Numerous attempts have been made to distinguish normal children from those with atrial septal defect and among those with atrial septal defect to predict the size of the shunt or right ventricular pressure. These attempts have been unsuccessful, with a few general exceptions. In atrial septal defects, the R′ wave tends to be slightly wider than normal; in children with an atrial septal defect with a small shunt, there is a deep S wave as compared with those with larger shunts or high pulmonary pressure, where both the R and R′ waves become taller and the S wave disappears. Specifically, atrial septal defect was more common in those less than 1 yr of age if the R′ wave was greater than 15 mm and in those older than 1 yr if the R′ was greater than 10 mm.[46,47] Despite these generalities, it may be im-

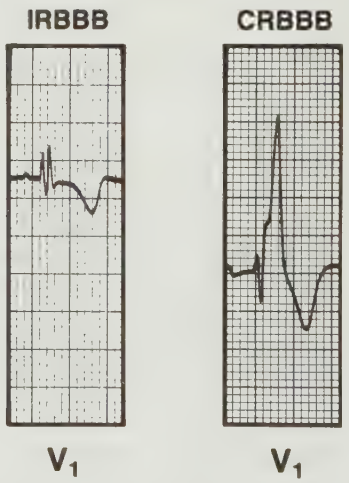


Fig. 45–35. Distinction of "incomplete" from "complete" right bundle branch block. Left: normal duration RSR′ complex. There is no break. The duration of the R wave and R′ wave are almost the same. This is the incomplete right bundle branch block pattern. Right: In the complete right bundle branch block pattern, there is a definite break and the R′ is three times the duration of the R wave.

possible to distinguish normal from atrial septal defect on the electrocardiogram in an individual patient.[48]

Left Bundle Branch Block

Complete Left Bundle Branch Block. Complete left bundle branch block results from delay in left ventricular activation. Since fibers of the left bundle branch initiate normal ventricular depolarization, if there is delay in left bundle branch conduction, the entire QRS complex is aberrant. This is different from the situation in right bundle branch block in which only the terminal portion is aberrant. In left bundle branch block, the right ventricle is activated first; therefore the normal initial vector, due to left to right septal spread, is absent. The slow activation of the left ventricle occurs from the right ventricle and the resultant slurred QRS complex is directed to the left, posteriorly and superiorly. The criteria for complete left bundle branch block are abnormally wide QRS complex (greater than 0.09 sec at under 4 yr of age, or greater than 0.10 sec from 4 to 16 yr), absent normal initial forces (absent Q wave in leads I, aVL, and V_6), and notched, slurred QRS complexes directed leftward and posterior (in lead V_1 a QS or small R–deep S, and in lead V_6 a tall, notched R wave) (Fig. 45–36). The T waves in complete left bundle branch block are approximately 180° discordant from the QRS complex for the same reasons as in complete right bundle branch block.

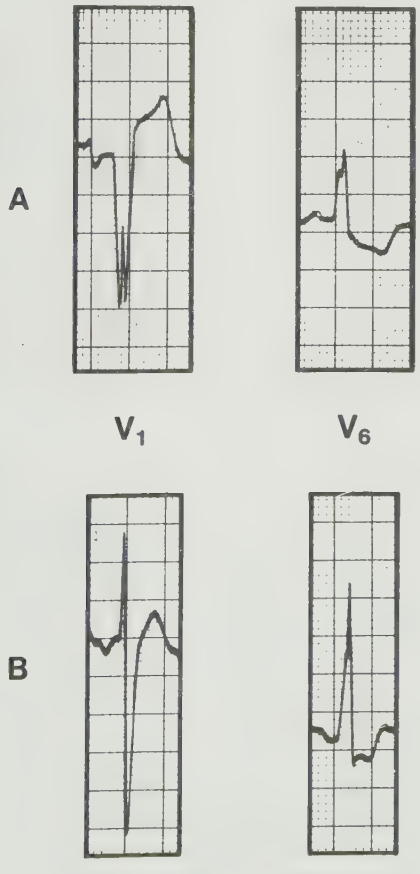


Fig. 45–36. Variations of complete left bundle branch block. In the top tracings (A), there is a QS pattern in lead V_1, and in the bottom tracings (B) there is an RS pattern in lead V_1. In lead V_6, both tracings are similar and marked by the absence of a Q wave.

The frontal-plane QRS axis in complete left bundle branch block is calculated based on the major deflection of the QRS complex. If the initial and terminal parts have different vectors, the terminal part of the complex should be used. Adults with left bundle branch block and left-axis deviation are more likely to develop complete atrioventricular block than those without left-axis deviation.[49] These data are not available for children.

Left bundle branch block is rare in children. The most common cause is surgery on the aortic valve or subvalve area. It may occur as a result of myocarditis, endocarditis, hypertrophic cardiomyopathy, or myocardial infarction.[38]

"Incomplete Left Bundle Branch Block" Pattern. Left ventricular hypertrophy may cause delayed left ventricular activation or stretching of the Purkinje fibers and produce a pattern of "incomplete left bundle branch block." The QRS duration may be normal or prolonged by 0.01 sec for age. There are absent Q waves and tall slurred R waves in leads I and V_6 (Fig. 45–37). On surface electrocardiograms, it is not possible to distinguish patients with incomplete left bundle branch block on the basis of left ventricular hypertrophy from those with mild conduction system disease.

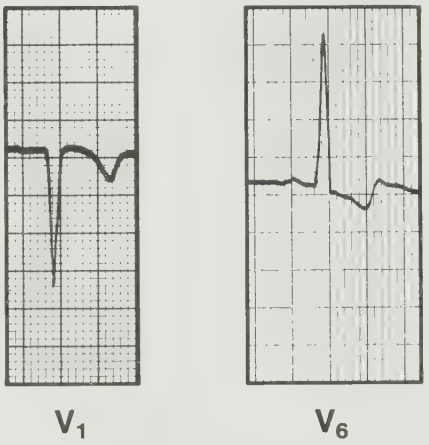


Fig. 45–37. Incomplete left bundle branch block pattern. There is an absent Q wave in lead V_6 and a normal QRS duration for this 11-yr-old child, and no R wave in lead V_1.

Fascicular Block

Although the anatomic correlation is not exact, there are patterns on the surface electrocardiogram that correspond to lesions in the anterior and posterior fascicles of the left bundle branch and these patterns are called left anterior hemiblock and left posterior hemiblock, respectively.

Left Anterior Hemiblock. The pattern of left anterior hemiblock results from asynchronous left ventricular activation where the posterior-inferior wall is activated before the anterior-superior wall, and there are two sequential vectors. The "earlier" activation of the posterior-inferior diaphragmatic surface of the left ventricle is directed inferiorly and slightly to the right at +120° in the frontal plane. The "later" activation occurs in the opposite direction when the anterior-superior wall is activated at −60° in the frontal plane (Fig. 45–38). The QRS duration is prolonged by less than 0.02 sec in pure left anterior hemiblock because part of the left ventricle is activated normally, and spread to the rest of the

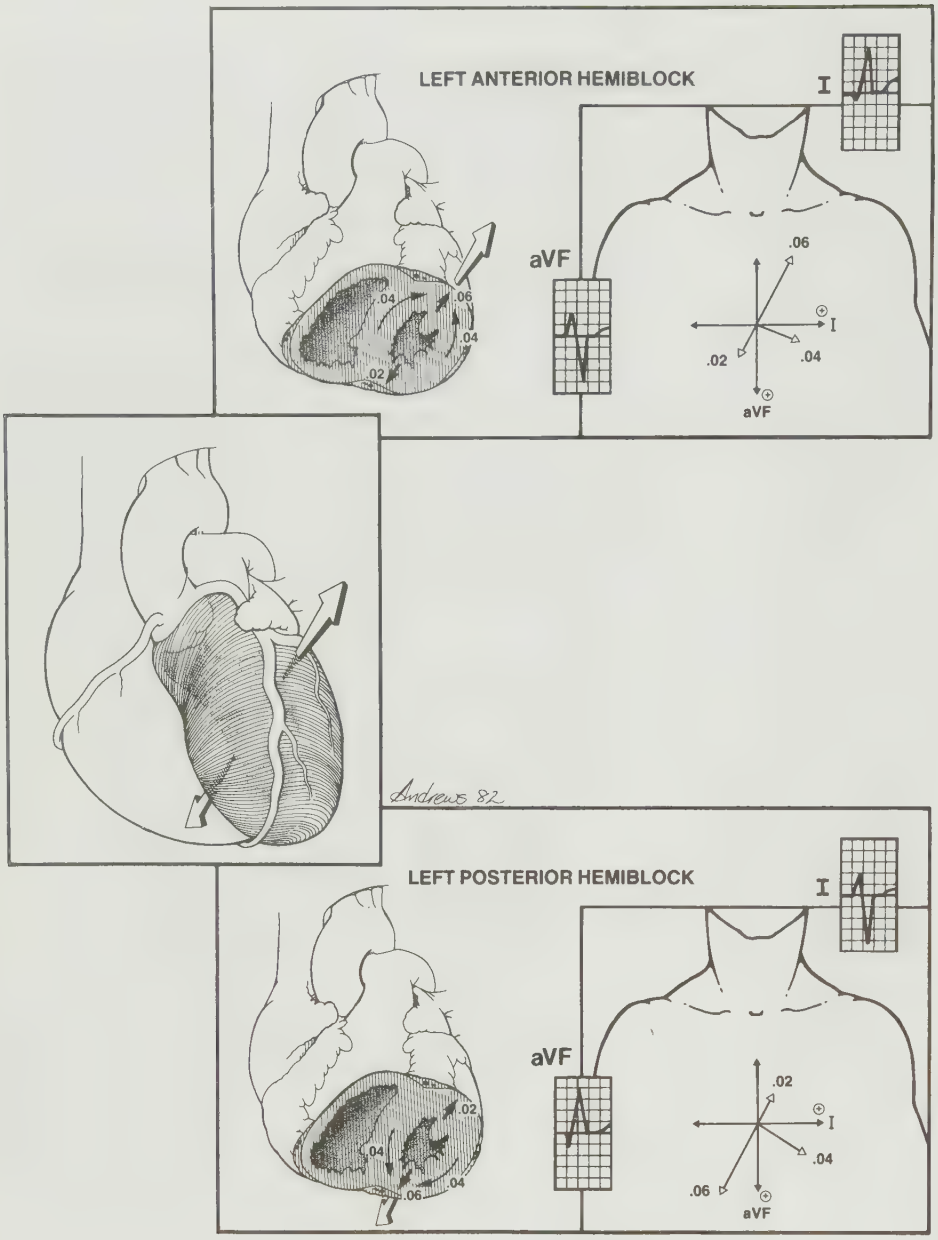


Fig. 45–38. Comparison of activation in left anterior hemiblock and left posterior hemiblock. (A) Left anterior hemiblock. The initial 0.02-sec vector is directed at +120° and the terminal 0.06-sec vector is directed at −60°. This causes an initial Q wave in lead I and a deep S wave in lead aVF. A coronal section through the heart is shown with the posterior-inferior wall activated before the anterior-superior wall. The mean QRS vector is directed superiorly as shown by the large arrow in the top diagram. (B) Left posterior hemiblock. The initial 0.02-sec vector is directed at −60° and the terminal 0.06-sec vector is directed at +120°. This causes a Q wave in lead aVF and a deep S wave in lead I. The anterior-superior wall is activated before the posterior-inferior wall. The mean QRS vector in the frontal plane is directed at +120° as shown by the large arrow in the bottom diagram. The orientation of the posteroinferior and anterosuperior walls are shown in the middle diagram.

left ventricle occurs relatively rapidly through the endocardium. The criteria for left anterior hemiblock are initial forces directed inferiorly and slightly to the right at +120°, major QRS forces directed superiorly and leftward (Left-axis deviation resulting from a horizontal heart position may give a QRS axis of −30°; therefore for the diagnosis of left anterior hemiblock, the frontal plane QRS axis must be to the left of −30°, i.e., negative in lead II; in most children with left anterior hemiblock, the QRS axis is −60°); and normal or minimally prolonged QRS duration (Fig. 45–39A). The T waves in left anterior hemiblock are normal.

In children, the most common cause of the left anterior hemiblock pattern is congenital heart disease. This may be due either to elongation of the left anterior fibers, to shortening of the left posterior fibers, or to a different orientation of the conduction system, such that the posterior left ventricular wall is activated before other parts of the heart.[50] These mechanisms may explain the left-axis deviation found in endocardial cushion defects (including ostium primum atrial septal defect, atrioventricular canal, and single atrium), single ventricle, and double-outlet right ventricle. Recent observations on tricuspid atresia suggest a different mechanism.[51] The activation times of the proximal left anterior and posterior fascicles were found to be normal, and it has been postulated that in tricuspid atresia, selective hypertrophy of the basal anterolateral left ventricle is responsible for sufficient conduction delay to cause the pattern of left anterior hemiblock on the surface electrocardiogram.[52] In anomalous left coronary artery, the left-axis deviation frequently observed may also be due to selective hypertrophy of noninfarcted superior portions of the left ventricle. This mechanism may also account for the occasional left-axis deviation found in aortic stenosis, aortic insufficiency, or cardiomyopathy. Isolated injury to the left anterior fascicle resulting in left anterior hemiblock from myocarditis has been

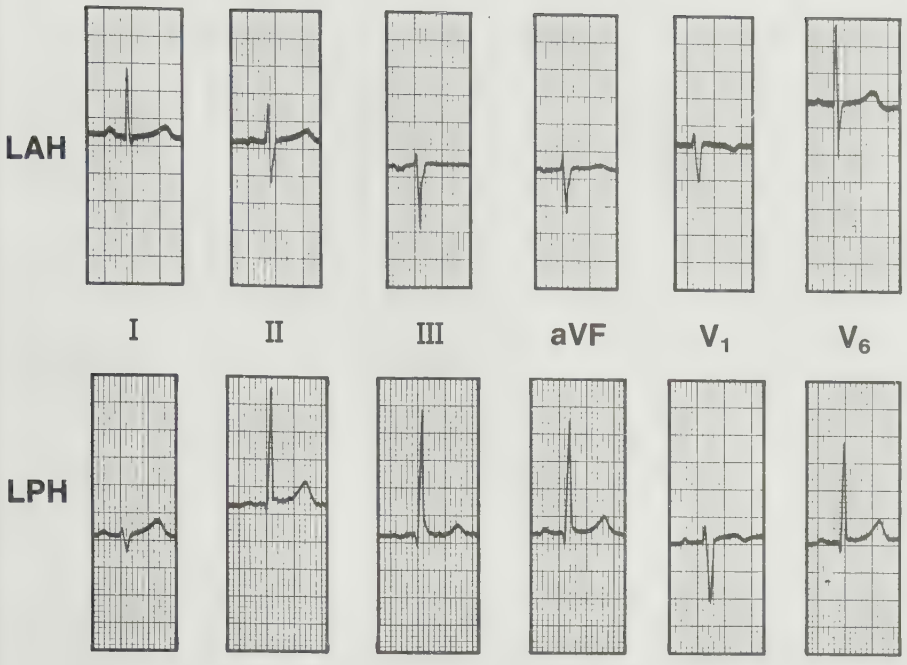


Fig. 45–39. Comparison of the electrocardiograms of left anterior hemiblock (top) and left posterior hemiblock (bottom). Note the absence of right ventricular hypertrophy in this 15-yr-old with left posterior hemiblock.

postulated as the cause of the left-axis deviation observed in up to 50% of infants with the rubella syndrome. Left anterior hemiblock may also result from myocardial infarction, ventricular septal myectomy, aortic valve surgery, or subvalvar aortic resection. Usually in closure of a ventricular septal defect, the left anterior hemiblock is accompanied by right bundle branch block (see section on "Bifascicular Block"). Left anterior hemiblock may rarely be familial and occur in otherwise normal children.[42]

Left Posterior Hemiblock. The activation sequence in left posterior hemiblock is exactly the opposite of that found in left anterior hemiblock (see Fig. 45–38B). The anterior-superior wall is activated first with a frontal plane QRS axis of $-60°$ and the posterior-inferior wall is activated last with a frontal plane QRS axis of $+120°$. The criteria for left posterior hemiblock are initial forces directed superiorly (Q waves in leads II, III, and aVF), major frontal-plane QRS forces directed inferiorly and rightward with an axis of $+90°$ to $+180°$, and normal or minimally prolonged QRS duration (Fig. 45–39B). This constitutes a normal electrocardiogram in most children and so left posterior hemiblock is difficult to diagnose. Left posterior hemiblock can be diagnosed if the frontal-plane QRS axis is between $+120°$ and $180°$ in a child over the age of 1 yr who does not have right ventricular hypertrophy or right atrial enlargement (i.e., another reason for right-axis deviation). Left posterior hemiblock is quite rare in children and has been diagnosed mainly in cases due to surgical trauma, myocarditis, or endocarditis.[53]

Bifascicular Block

Considering the trifascicular conduction system as the left anterior fascicle, left posterior fascicle, and right bundle branch, bifascicular block is blockage in any two of the three fascicles. In the strict sense of the term, complete left bundle branch block is a form of bifascicular block. The combination of right bundle branch and left posterior hemiblock is practically never diagnosed in children because the right bundle branch block is most often the result of an operation on a lesion with preexistent right ventricular hypertrophy and right-axis deviation. Therefore, in children, the term bifascicular block is almost synonymous with right bundle branch block plus left anterior hemiblock.

Right Bundle Branch Block–Left Anterior Hemiblock Pattern. Left anterior hemiblock changes the first "fast" part of the QRS complex and right bundle branch block changes the terminal "slow" part. The criteria are initial forces (first 0.02 sec) directed inferiorly and rightward at $+120°$ in the frontal plane giving a Q wave in lead aVL and possibly lead I, major axis of the "unblocked" initial part of the QRS complex to the left of $-30°$ giving a dominant S wave in the initial part of lead II and possibly leads V_5 and V_6, and slurred terminal portion of right bundle branch block directed to the right (Fig. 45–40).

The most common cause of right bundle branch block and left anterior hemiblock in children is surgery for tetralogy of Fallot, and occurs in approximately 10% of such patients.[54] This pattern may also occur in any injury to the area of the distal His bundle or proximal right bundle branch, since the right bundle branch and left anterior fascicle lie in such close proximity. This pattern may also be seen after other intracardiac operations involving surgery near the atrioventricular junction, or it may be found in myocarditis, cardiomyopathy, and endocarditis. Familial bifascicular block occurs and may progress to complete atrioventricular block.[55]

Trifascicular Block

Trifascicular block is defined as delay in all three fascicles. It can only be diagnosed by intracardiac electrograms as a prolonged H–V interval, and cannot be diagnosed on the surface electrocardiogram. The combination of right bundle branch block, left anterior hemiblock, and first-degree atrioventricular block has been erroneously termed trifascicular block. This combination has many different possible causes. Most children with this pattern have atrioventricular nodal delay and bifascicular block with a normal H–V interval.[56,57]

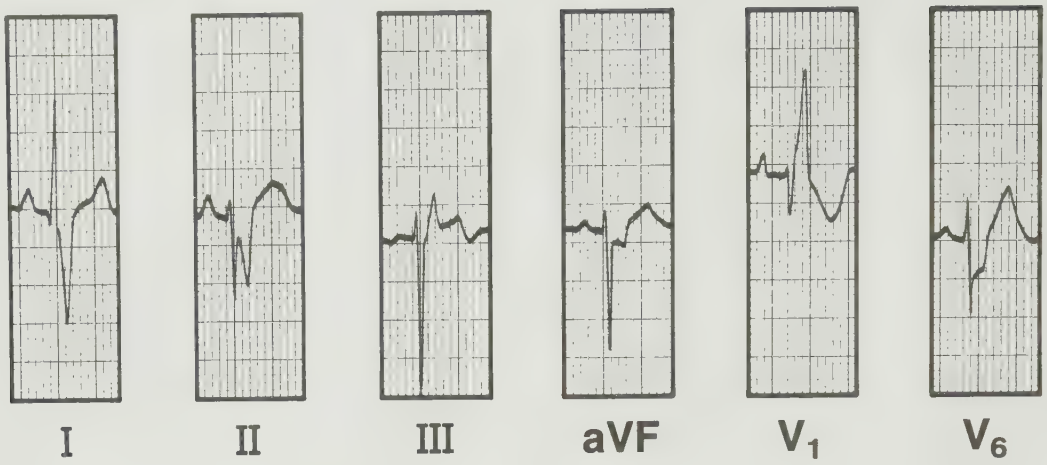


Fig. 45–40. Right bundle branch block with left-axis deviation.

Interventricular Conduction Delay

The QRS complex is prolonged for age but has no specific pattern of right bundle branch block or left bundle branch block. This may be found in children with quinidine or procainamide toxicity, myocarditis, hypoglycemia, myocardial ischemia, or hyperkalemia (Fig. 45–41).[58]

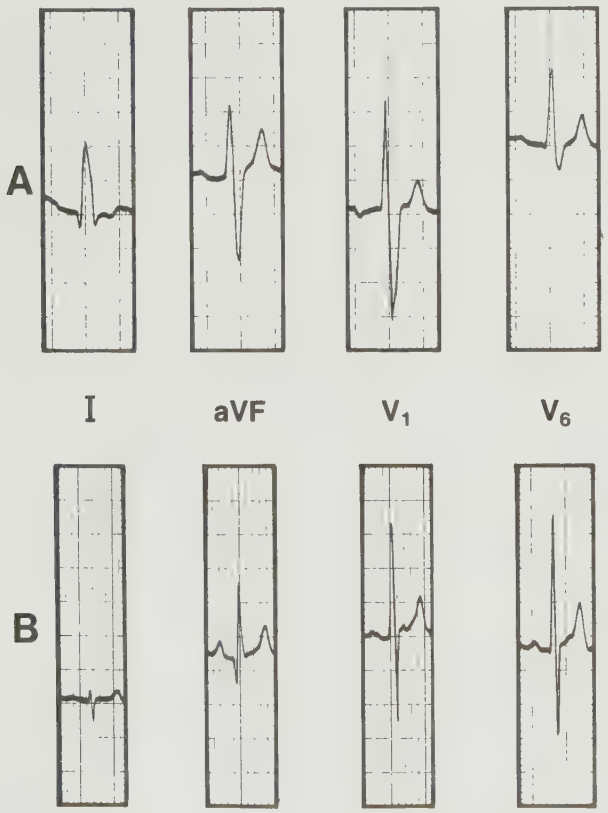


Fig. 45–41. Interventricular conduction delay. Top tracings taken from a 1-mo-old child with renal failure who was hyperkalemic. The bottom tracings were taken from the same child after dialysis. The QRS complexes are similar in comparison of the same leads but they have a prolonged duration in the top tracings.

Preexcitation

Preexcitation is defined as an abnormally rapid transit of the wave of depolarization from atria to ventricles. In most cases of preexcitation, the ventricles are activated asymmetrically from a point other than the bundle of His, in addition to being activated via the normal conduction system. Since atrioventricular conduction can occur by two possible pathways, usually with different properties, one of the possible consequences of preexcitation is reciprocating supraventricular tachycardia.

Wolff-Parkinson-White Syndrome

Wolff, Parkinson and White first described the syndrome of short P–R interval with a prolonged QRS duration in 1930.[59] It has since been demonstrated that the cause of this pattern is a direct muscular connection between the atria and the ventricles: "a Kent bundle" or "accessory atrioventricular connection." The accessory connection runs perpendicular to the atrioventricular ring and can be located anywhere around either valve orifice except the point of fibrous continuity between the mitral and aortic valves. Most Kent bundles conduct much faster than the atrioventricular node, so the atrial depolarization is transmitted to the ventricles prematurely, resulting in a short P–R interval. The ventricles than begin to depolarize from the point of insertion of the accessory connection. If there was no atrioventricular nodal conduction and the ventricles were completely excited by the accessory connection, the QRS complex would appear similar to a premature ventricular contraction that originated at the site of insertion of the accessory connection. However, in the majority of cases, the atrioventricular node also conducts the impulse from atria to ventricles, and the depolarization wave resulting from the accessory connection and the atrioventricular node collide in the ventricles causing a "fusion" QRS complex (Fig. 45–42). The characteristics of this complex are that the beginning is more slurred (resulting from eccentric slow ventricular activation by the accessory connection) and the end of the complex is more normal (resulting from normal ventricular activation via the His bundle and bundle branches). In any individual child, the amount of the ventricles activated via the Kent bundle and the His bundle can vary from day to day; this accounts for our observation that one third of children with

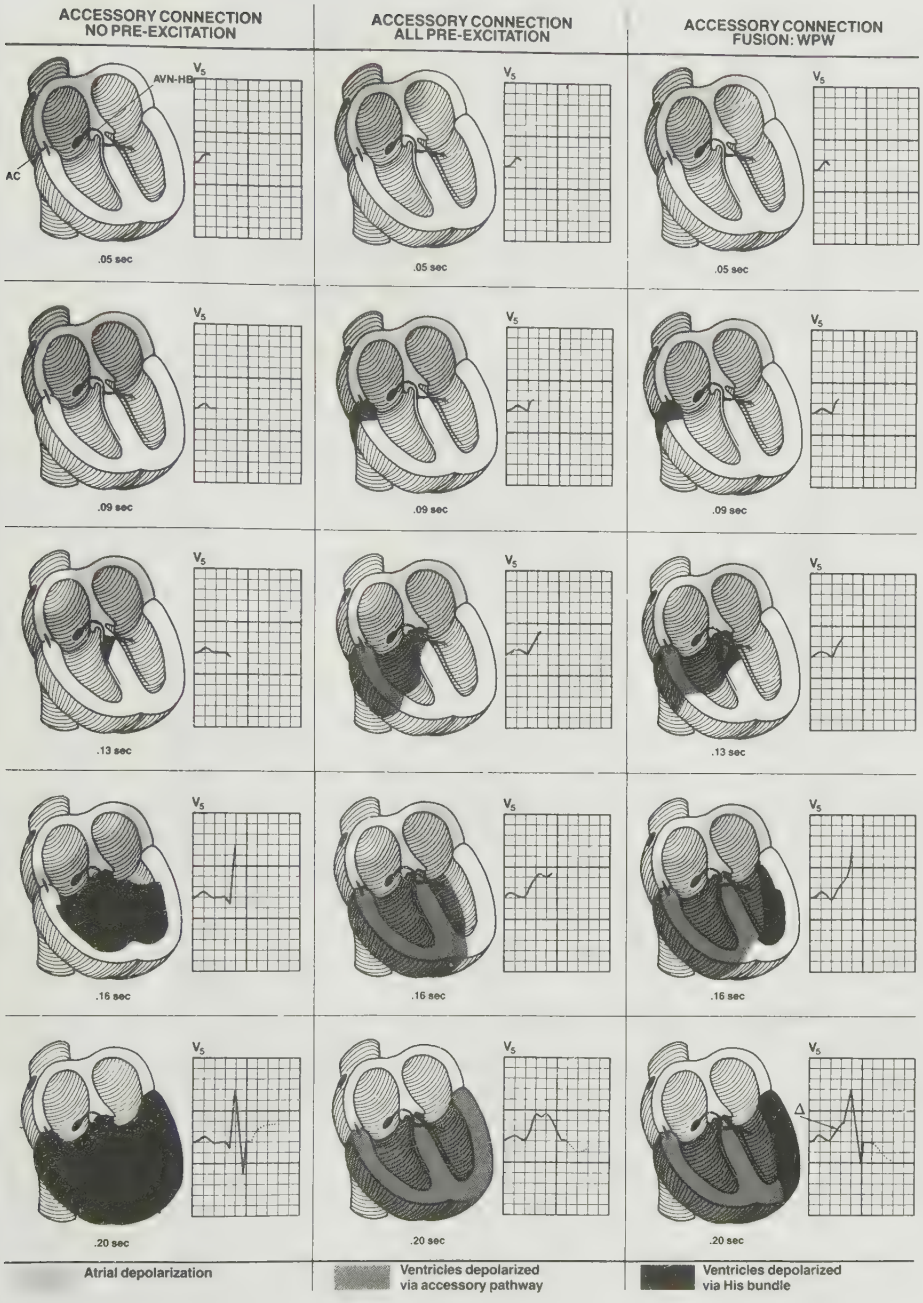


Fig. 45–42. Wolff-Parkinson-White syndrome with varying degrees of conduction through the accessory connection and the atrioventricular node. The numbers refer to timing after the onset of the P wave. The left column of diagrams indicates the activation sequence in the patient with an accessory connection who is not conducting through the accessory connection but entirely through the atrioventricular node. Note the normal P–R interval, the Q wave, and the lack of a delta wave. In the middle column, the activation sequence of a patient who is conducting entirely through the accessory connection are shown. Note the short P–R interval and the wide QRS complex. There is no real "delta" wave because the entire QRS complex is wide. In the right column, the usual situation of Wolff-Parkinson-White syndrome is shown, in which there is a "fusion" complex resulting from conduction through both the accessory connection and the atrioventricular node. The parts of the ventricles activated through the atrioventricular node are shaded differently in the diagrams from those activated by the accessory connection. Note that there is a short P–R interval and a delta wave (indicated by the "delta" at 0.16 sec in the right column of diagrams). The delta wave occurs because there is fusion of the completely wide QRS with the completely narrow QRS, causing an abrupt change in slope.

Wolff-Parkinson-White syndrome had at least one electrocardiogram without any preexcitation (normal P–R interval and normal QRS complex), which was later followed by the reappearance of Wolff-Parkinson-White syndrome.

The criteria for Wolff-Parkinson-White syndrome are short P–R interval for age (see Table 45–1), and a QRS complex with initial slurring—the "delta wave." All electrocardiographic leads may not show a short P–R interval and delta wave if the vector of the delta wave is perpendicular to that lead (see Fig. 45–6). Rosenbaum classified the Wolff-Parkinson-White pattern on surface electrocardiograms into types A and B in an attempt to predict localization of the Kent bundle.[60] In type A, the major QRS deflection is positive in lead V_1, predicting a left lateral accessory connection (Fig. 45–43A). This simulates right bundle branch block, but the two can be distinguished, since the initial forces in Wolff-Parkinson-White syndrome are slow in comparison to the rapid initial forces in right bundle branch block. In type B, the major QRS deflection is negative in V_1, predicting a right-sided accessory connection (Fig. 45–43B). This simulates left bundle branch block, except that usually Wolff-Parkinson-White syndrome has normal terminal forces. Despite the general helpfulness of this classification scheme, we have not found that the exact site of the accessory connection can be predicted from the 15-lead surface electrocardiogram. Since Wolff-Parkinson-White syn-

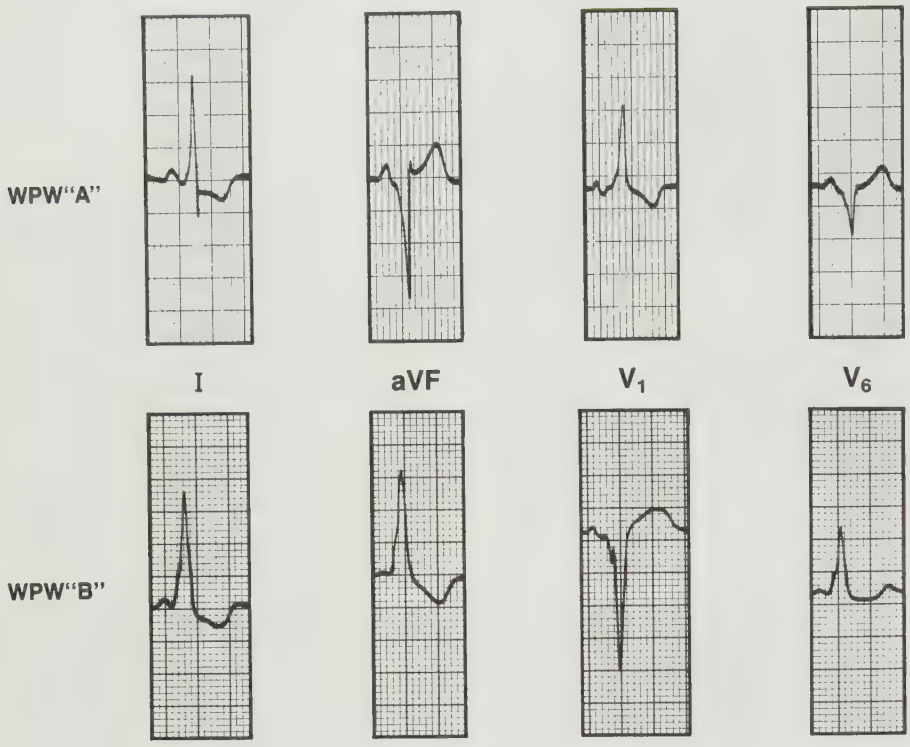


Fig. 45–43. Wolff-Parkinson-White syndrome. (A) Rosenbaum "type A." (B) Rosenbaum "type B."

drome is more common in children than left bundle branch block, in any child with a pattern similar to left bundle branch block, the P–R interval should be measured carefully.

Lown-Ganong-Levine Syndrome

Lown, Gangong, and Levine described the syndrome of short P–R interval without a delta wave in sinus rhythm in 1952.[61] All their cases had associated supraventricular tachycardia. Although it does not cause interventricular conduction disturbance, we have included Lown-Ganong-Levine syndrome in this section because by our definition it results in ventricular preexcitation (Fig. 45–44). Lown-Ganong-Levine syndrome should probably not be diagnosed in the absence of supraventricular tachycardia, since a short P–R interval may be found in normal children without a predisposition to supraventricular tachycardia.[62]

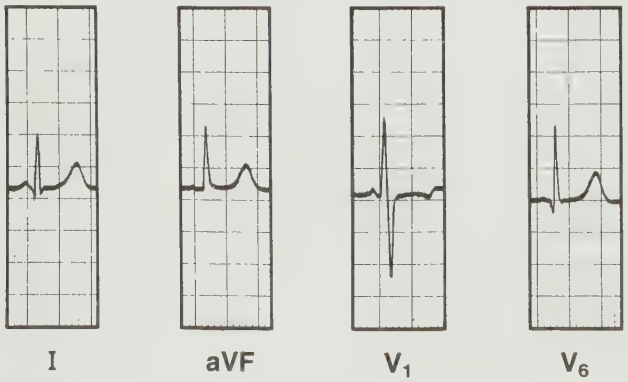


Fig. 45–44. Lown-Ganong-Levine syndrome. The P–R interval is short and the QRS complex is normal in all leads.

Short PR intervals are also observed in mannosidosis, Fabry's disease, and Pompe's disease.[63,66] All these diseases may have in common an increase in cell size in the atrioventricular node; this may be related to rapid atrioventricular nodal conduction.[64] Patients with these diseases do not appear to be at risk for supraventricular tachycardia.

Mahaim Conduction

Mahaim and Benatt first described muscular connections between the His bundle and ventricular septum in 1938.[67] The definition of a Mahaim fiber has been broadened to include a fiber that originates in the atrioventricular node, His bundle, or proximal bundle branch and inserts in the ventricular muscle. This is a "bundle branch bypass" tract and results in preexcitation. Usually, the bundle inserts into the right ventricle, giving a left bundle branch block morphology to the QRS complex.[68] As conduction can also occur via the normal pathway (His bundle and bundle branches) and through the Mahaim fiber, there may be a fusion QRS complex similar to that seen in Wolff-Parkinson-White syndrome. In many cases, the QRS complex is normal in sinus rhythm. However, with a Mahaim fiber, the P–R interval is normal (Figs. 45–45 and 45–46). Since two pathways exist with different properties, reciprocating supraventricular tachycardia can occur with a left bundle branch block morphology due to antegrade activation via the Mahaim fiber.

ISCHEMIA, INJURY, AND INFARCTION

The major changes that occur with ischemia, injury, and early infarction involve the T waves and ST segments.

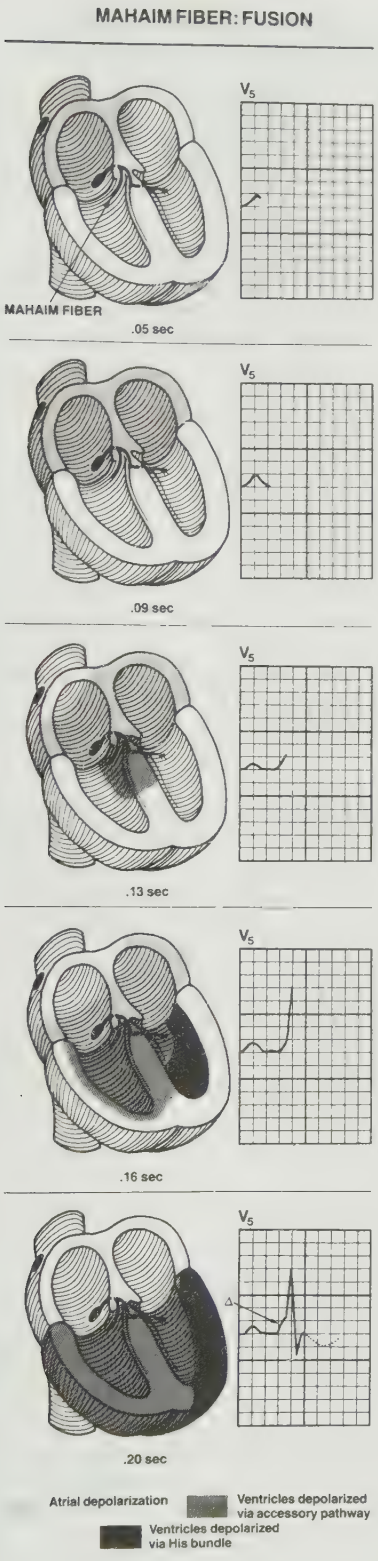


Fig. 45–45. Mahaim conduction. Interventricular conduction is shown for a Mahaim fiber. The P–R interval is normal and there may be a delta wave resulting from fusion of the impulse passing through both the Mahaim fiber and the atrioventricular node.

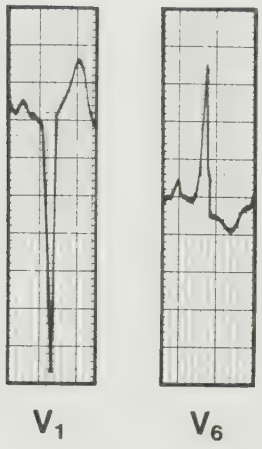


Fig. 45–46. Mahaim conduction. The P–R interval is normal and there is a delta wave in lead V_6. The morphology of this complex is similar to left bundle branch block.

Primary and Secondary T-Wave Changes

Primary T-wave changes occur when repolarization is affected, independent of changes in depolarization. These may occur either with uniform alteration in the shape or duration of all action potentials without a change in the sequence of depolarization (e.g., hyperkalemia), or with nonuniform changes in the shape or duration of the action potentials in different parts of the ventricle, resulting in an altered sequence of repolarization (e.g., localized ischemia). The majority of the primary T-wave changes occur with ischemia or other systemic alterations that have an effect on the heart.

Secondary T-wave changes occur when altered repolarization is caused by an abnormal sequence of depolarization. In children, these are much more common than primary changes and occur in such conditions as bundle branch block, preexcitation and hypertrophy. Frequently, a secondary T-wave change is mistaken for a primary change because the minor QRS abnormality responsible for the secondary change is not recognized. Minor changes in the duration and shape of the QRS complex, especially in the terminal portion, may be responsible for significant secondary T-wave changes. Therefore, before assigning a T-wave change to the primary category, it is important to be sure the changes cannot be explained by an abnormal QRS complex.[4]

Functional T-Wave Changes

The majority of these changes appear to have a link to the sympathetic nervous system. Fear and anxiety are known to cause inverted T waves without a change in coronary blood flow.[69] Sympathetic mechanisms are thought to be responsible for the T-wave changes in hyperventilation. Ten percent of teenagers had inverted T wave in at least one chest lead after 10 to 15 sec of hyperventilation and 70% had inverted T waves after 45 sec.[70] The degree of alkalosis or hypocarbia could not be related to the T-wave changes. Orthostatic T-wave changes have been described in the inferior leads in 3% of normal adults who stand up after lying down for several minutes.[4] It is not known whether the postural change is due to catecholamines or a physical shift of the heart. Approximately 4% of normal adults develop flat or inverted T waves in several leads within 30 min of eating a high-carbohydrate

meal or drinking a high-concentration glucose solution. If a child has flat or inverted T waves without a known cause, the electrocardiogram might be repeated in the postabsorptive state.[8]

There are two other functional changes that are most common in adolescence. The "early repolarization syndrome" is recognized by J-point elevation in several leads and may mimic true ST elevation. Usually, the T waves in early repolarization are very large. This pattern is due to the early appearance of the T wave while the ventricles are still depolarizing.[71] This eliminates the ST segment. Sympathetic stimulation either by exercise or isoproterenol infusion generally normalizes the J-point elevation (Fig. 45–47). Alternatively, in the asymptomatic patient, one can wait for several days and check another electrocardiogram. In early repolarization, the J-point elevation is persistent, whereas in pericarditis, the other common cause of elevated ST segments in children, the changes evolve.

The second functional T-wave change found in adolescence is the isolated inverted T wave in a midprecordial lead with an upright T wave in the leads on either side. This occurs in 1% of adolescents and has no pathologic correlate.[69] In general, benign T-wave changes are labile.[72]

Ischemia

Myocardial ischemia is manifest electrocardiographically by distortion of the T-wave amplitude, configuration, and axis. The first area to become ischemic in the heart is generally the subendocardium, and in cases of subendocardial ischemia, the T wave points toward the normal epicardial tissue overlying the ischemic area. In subendocardial ischemia, the T waves are symmetrical and peaked, with an increase in amplitude and duration in the leads overlying the ischemic area. In subepicardial ischemia, the T waves are inverted, overlying the ischemic area. In transmural ischemia the T waves are inverted, overlying an area of transmural ischemia.

Myocardial ischemia is rare in children. It can occur in the early stages of reduced coronary blood flow from neonatal stress, anomalous left coronary artery, or mucocutaneous lymph node syndrome (Kawasaki's disease) before infarction occurs. Subendocardial ischemia may occur in children with aortic stenosis or pulmonary stenosis. The flattened or inverted T waves that accompany rapid sinus tachycardia or supraventricular tachycardia may be due to ischemia but they may also be secondary T-wave changes attributable to minor degrees of ventricular aberration obscured by the rapid rate. The persistence of these T-wave changes up to days after the event may be related to potassium loss with slow replenishment of metabolic stores.[71] In 10% of children with mitral valve prolapse, there is T-wave inversion in the inferior and lateral leads. These changes may be explained either by the presence of small ischemic areas due to traction interfering with the vascular supply or by uneven repolarization.[8] Other changes with mitral prolapse include a prolonged Q–T interval and prominent U waves.[73]

In pure left ventricular hypertrophy, the usual electrocardiographic pattern is an increase in the T-wave amplitude; in advanced left ventricular hypertrophy, there is ST depression with inverted T waves—the "strain" pattern.[74] Thus "strain" is different from subendocardial ischemia, in which there is ST depression and upright or flat T waves. It has been suggested that "strain" is a primary T-wave abnormality, is due to a difference in endocardial and epicardial conduction times, and has a different mechanism from ischemia.[75] Alternatively, the ST–T-wave changes observed in hypertrophy and strain may be simply more severe changes in a spectrum from subendocardial to transmural ischemia.

Injury

Myocardial injury is evidenced electrocardiographically both by deviations from the base line and changes in the contour of the ST segment. In subepicardial injury, an electrode immediately over the area of injury shows ST elevation. In subendocardial injury the electrode immediately over this area shows ST depression. Thus, with injury, the ST segment is displaced toward the injured surface. When the ST segment is elevated, the contour may be either upwardly convex or concave; with ST depression, the contour is usually concave or flat. In children, injury patterns that are not due to systemic alterations are found most frequently in pericarditis and ischemic episodes.

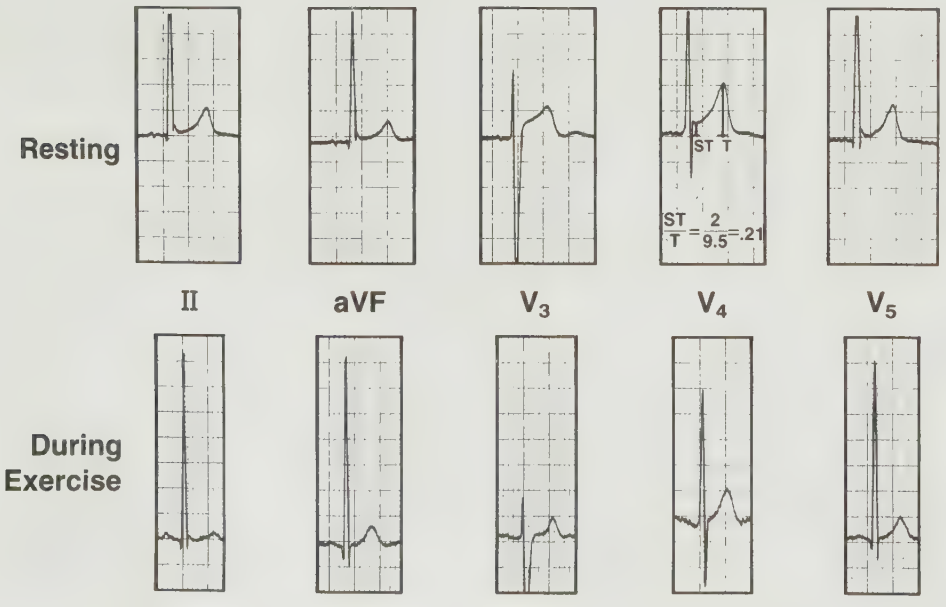


Fig. 45–47. Early-repolarization syndrome. In the resting electrocardiogram shown at the top, there is J-point elevation in the inferior and lateral leads. In this patient, leads I and aVL were normal. There was 1 mm of J-point depression in aVR. After 6 min of treadmill exercise, the bottom tracings were taken, showing normalization.

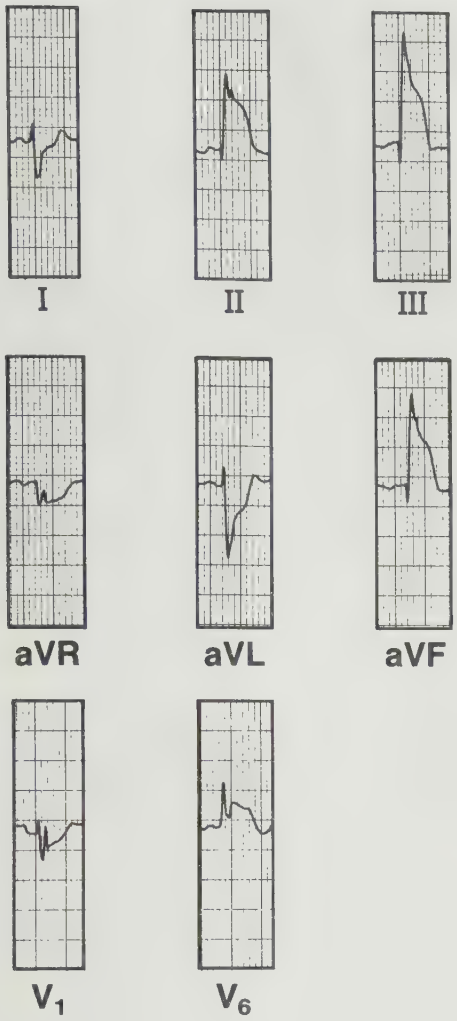


Fig. 45–48. Acute inferior myocardial infarction in a 3-mo-old child with staphylococcal sepsis. At autopsy, there was extensive abscess in the left ventricle. There is considerable ST elevation in leads II, III, and aVF. There is reciprocal ST depression in leads I, aVL, aVR and V_1.

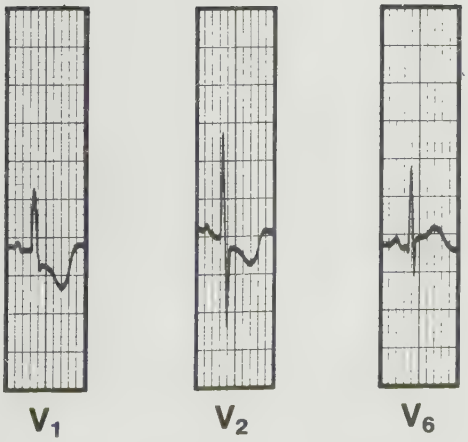


Fig. 45–49. ST-segment shift with patent ductus arteriosus. This tracing was taken from an 840-g infant with cardiomegaly due to a patent ductus arteriosus. Note the ST depression in leads V_1 and V_2 and ST elevation in lead V_6. The ST–T-wave changes resolved after ductus ligation.

Injury due to Ischemia

It is rare to obtain an electrocardiogram from an infant or child who is undergoing an acute myocardial infarction, but this diagnosis should be included when considering ST elevation (Fig. 45–48). A more common kind of ST-segment shift seen in children is the ST depression found in some infants with patent ductus arteriosus (Fig. 45–49). In 15 of 19 severely ill infants who required patent ductus arteriosus ligation, ST depression of 2.5 to 10 mm was found in leads V_1 and V_2. The ST change disappeared after ligation of the ductus. The explanation for these changes is a marked myocardial oxygen supply–demand imbalance primarily in the right ventricle: The supply is reduced due to the low aortic diastolic pressure with reduced coronary flow and the myocardial oxygen demand is increased due to the high pulmonary artery systolic pressure.[76]

Injury due to Myocarditis

Cellular injury occurs with myocarditis. Approximately 70% of children with myocarditis have electrocardiographic changes.[77] An abnormal electrocardiogram implies myocardial damage; however, a normal electrocardiogram does not preclude severe injury. The electrocardiogram may normalize within 2 to 3 weeks of the onset of the disease, but it may remain abnormal for up to 4 mo with later reversion to normal. A normal electrocardiogram after myocarditis also does not preclude severe residual damage.[71]

The most prominent electrocardiographic changes are flat or inverted T waves (primarily in the left chest leads) and "low-voltage" QRS complexes (see the section on low QRS voltage under "The Normal Electrocardiogram"). The T-wave changes are probably due to altered repolarization of injured cells throughout the myocardium rather than to true ischemia. The Q–T interval may be prolonged. The low-voltage QRS complex results from myocardial edema. Myocarditis also commonly results in ST depression due to extensive subendocardial injury. ST elevation is rare in myocarditis without pericarditis.[78] There have been several reports of the appearance of new Q waves in association with myocarditis. These have mostly been in children who later died. The Q waves were accompanied by ST elevation in those patients. There was no characteristic electrocardiographic location for these changes. In different children, the Q waves were in the inferior, lateral, or anterior leads (Fig. 45–50). Pathologic studies have documented extensive areas of necrosis and scarring that correlate with the electrocardiographic location of the Q waves in these patients.[79,80]

Atrioventricular block and interventricular conduction delay may occur in any type of myocarditis, but right bundle branch block is particularly common to the myocarditis due to Chagas' disease. Premature ventricular contractions occasionally occur in myocarditis.[71]

Injury due to Pericarditis

Pericarditis is by far the most common pathologic cause of ST elevation in children. Other causes of primary ST changes include myocardial infarction, cor pulmonale, head injury, digitalis, hy-

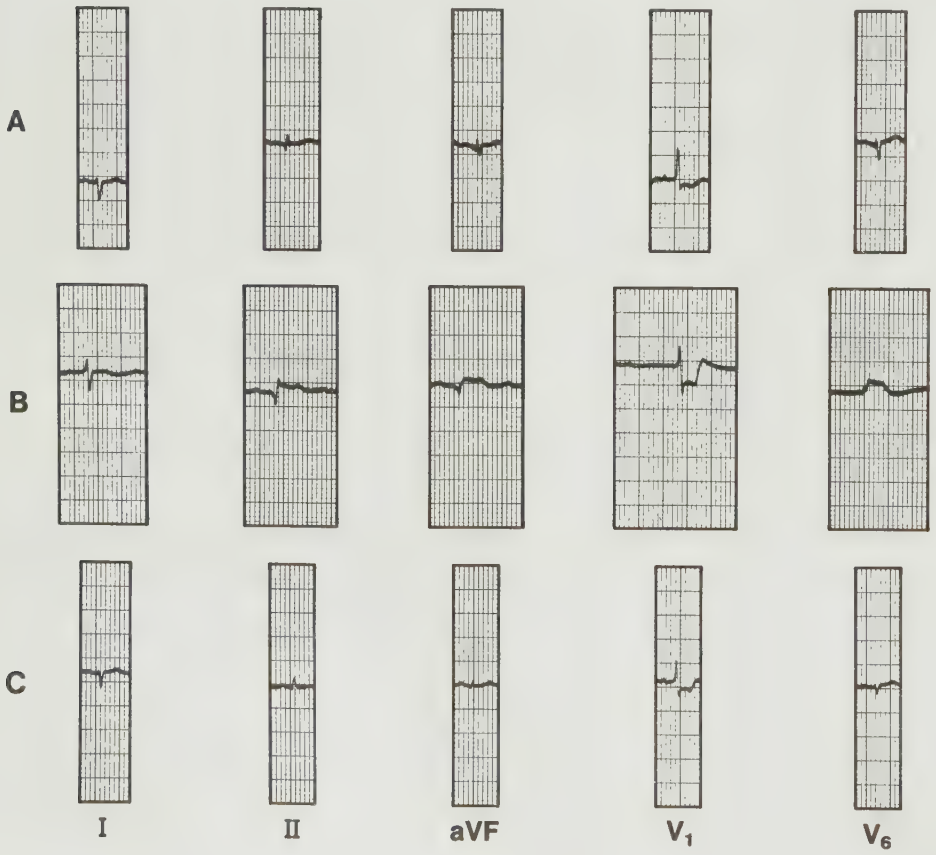


Fig. 45–50. Myocarditis in a 1-wk-old infant. (A) Low-voltage QRS complexes in both the limb leads and precordial leads. The T waves are concordant but decreased in amplitude. (B) Twelve hours later, complete atrioventricular block and deep, wide Q waves in leads III and aVF develop, accompanied by ST elevation in leads III, aVF, and V_6, with ST depression in lead V_1. This is compatible with an inferolateral myocardial infarction. (C) On the next day the infant has evidence of even less voltage in the inferior and lateral leads. He died the following night and was shown at autopsy to have diffuse areas of myocarditis and areas of necrosis throughout both ventricles.

perkalemia, emetine intoxication, pneumothorax, pneumopericardium, early ventricular repolarization, and normal atrial repolarization.

The electrocardiogram in pericarditis characteristically evolves through four stages (Fig. 45–51), as described below.

Stage 1, ST Elevation. This is thought to be due to subepicardial myocarditis. The ST elevation occurs in leads facing the epicardium (leads II, aVF, and V_3 to V_6). Depending upon the position of the heart, lead I or III may also be involved. The leads without epicardial representation, which are usually facing away from the left ventricle (leads aVR and V_1), may show reciprocal ST depression. In neonates, the right ventricle constitutes more of the epicardial surface, and the right chest leads may show ST elevation with the left chest leads showing ST depression.[71]

Pericarditis can usually be differentiated from acute myocardial infarction. In pericarditis, the ST elevation is found in numerous leads, whereas in myocardial infarction it is generally limited to a few leads. Also, the ST elevation in pericarditis is associated usually with an upright T wave, whereas in myocardial infarction, beyond the hyperacute phase, the T wave is usually inverted. In pericarditis during the time of ST elevation, it may also be possible to detect P–R segment elevation (greater than 0.8 mm) due to atrial subepicardial injury in leads overlying the right atrium (aVR and V_1) and reciprocal P–R depression (greater than 0.5 mm) in leads normally showing ST elevation.[8]

Stage 2. Stage 2 is characterized by normalization of ST segments with T-wave flattening. This occurs as an intermediate to stages 1 and 3.

Stage 3. In stage 3, there is T-wave inversion in the same leads in which the ST elevation previously appeared.

Stage 4. Stage 4 is resolution.

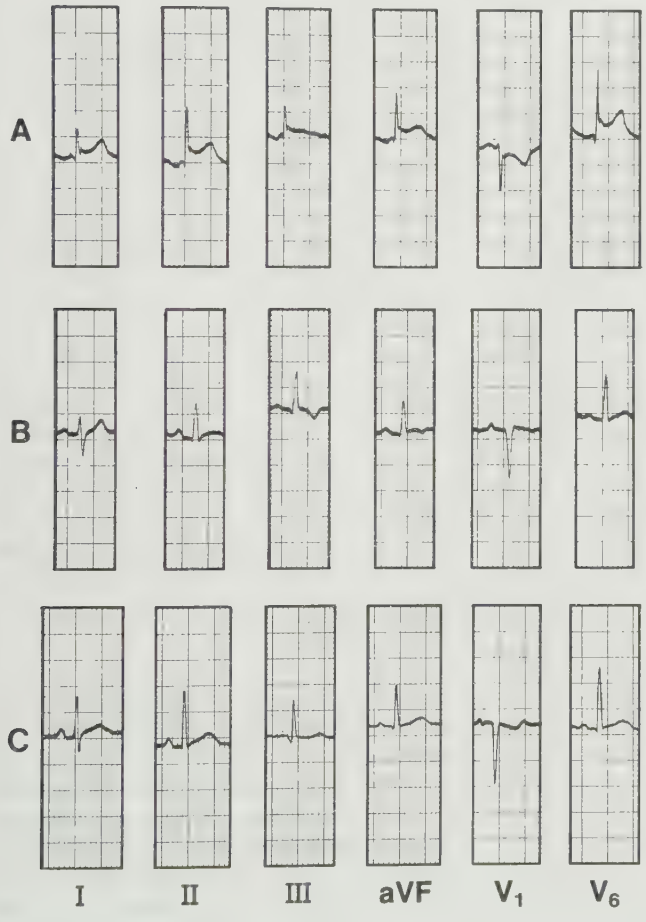


Fig. 45–51. Evolution of pericarditis in a 12-yr-old. (A) ST elevation with upright T waves in all leads except V_1. (B) The ST elevation is resolving and is replaced with T-wave inversion in leads III and aVF. This electrocardiogram was taken 4 days after the first one. (C) Two weeks later the ST–T-wave changes are resolved, but there is a Q wave in lead III that is wider than on previous tracings. This could indicate a small area of old inferior myocardial infarction.

In a prospective study of adults, 92% had electrocardiographic changes in pericarditis. In only half of these, typical ST elevation occurred, followed by T-wave inversion. In those without preceding ST elevation, T-wave inversion did not occur. P–R segment elevation occurred in 64% of these adults, and in 10% this was the only change of pericarditis.[81] The QRS complex is generally not affected by pericarditis. Even in the presence of a large pericardial effusion, the QRS may have normal voltage in pericarditis.[8]

Infarction

Infarcted muscle is electrically inert. The loss of electrical forces normally generated by the region of infarcted myocardium leaves unbalanced forces of unaltered magnitude in the opposite direction, resulting in Q waves overlying the area of infarction (Fig. 45–52). The earliest electrocardiographic manifestations of myocardial infarction are "hyperacute" very tall, peaked T waves. Hyperacute T waves occur in the first minutes, and are therefore infrequently observed. Soon thereafter, ST elevation is observed in leads overlying the infarction and a current of injury to that area is displayed. There may be reciprocal ST-segment depression in leads opposite the infarction. Within several hours to days, the ST elevation is typically followed by the development of Q waves and inverted T waves in leads overlying the infarction. Q waves of myocardial infarction in children are wide (0.04 sec or more), similar to those found in adults (Fig. 45–53). In children, Q waves related to myocardial infarction may disappear. As growth occurs, the infarcted area may become smaller relative to the greater total mass of the heart.

Anomalous Left Coronary Artery Originating from the Pulmonary Artery

In infancy, wide Q waves are more prominent than in later childhood.[82] Q waves are almost invariably present in lead I and are usually present in lead aVL, and may extend from the midprecordial to the lateral precordial leads (V_3 to V_6). There may be an abrupt loss of R wave in the midprecordium with a normal R wave in V_1, V_6, and V_7. In the frontal plane, the QRS mean vector is usually $+90°$.[47] The T waves are usually inverted in leads I and aVL and the lateral precordial leads. In older children, the Q waves become less prominent, resulting in compensatory hypertrophy of the posterobasal left ventricle. The major terminal QRS vector is superior, left, and posterior, frequently causing left-axis deviation in the frontal plane. There may be loss of the normal right ventricular dominance and deep S wave in leads II, III, aVF, and V_1 with tall R waves in leads aVL, V_5, and V_6. The T waves

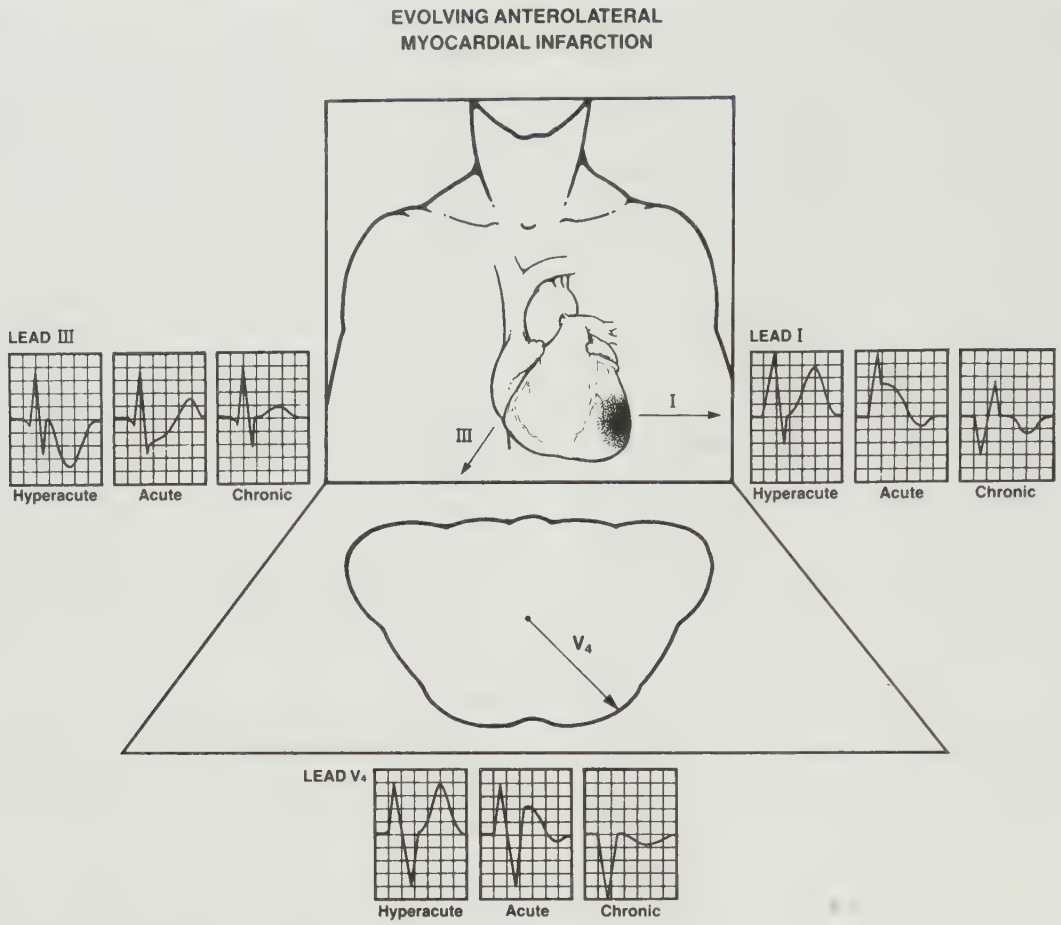


Fig. 45–52. Evolution of an anterolateral myocardial infarction.

are discordant in leads I, V_1, and V_6. While this evolution is characteristic, an individual patient may present with any combination of these findings (Fig. 45–54).

Papillary Muscle Infarction

Newborn infants with severe neonatal stress, or infants with severe pressure or volume overload may develop papillary muscle infarction. Characteristic electrocardiographic findings have been found in infants with aortic stenosis or total anomalous pulmonary venous return who were proven at autopsy to have had anterior papillary muscle infarction of either the right ventricle or left ventricle. In these infants, Q waves were present in lead V_3R. There was also a progressive diminution of the R wave in lead V_3R on serial electrocardiographic tracings.[83] This is to be distinguished from the other major causes of Q waves in the right chest leads in infancy—severe right ventricular hypertrophy or reversed septal depolarization from ventricular inversion.

Kawasaki's Disease

Kawasaki's disease (mucocutaneous lymph node syndrome) is the most common acquired cause of myocardial infarction in infants and children. The Q waves that occur in Kawasaki's disease are abnormally deep (especially in the inferior leads) and are usually abnormally wide (especially in the lateral leads).[84] Abnormally deep Q waves are defined in the section on "The Normal Electrocardiogram." Q waves may develop in the first 2 weeks of the illness and may be due to severe myocarditis. These may subsequently resolve. If Q waves develop later than 2 weeks into the illness, this is usually associated with a coronary artery aneurysm and myocardial necrosis. In some patients, a serial deepening of the Q waves was the only sign of infarction (Fig. 45–55). The absence of Q waves implies neither an absence of aneurysms nor an absence of significant areas of myocardial necrosis at autopsy.[84]

Pseudoinfarction

Other causes of abnormal Q waves, with or without ST–T-wave changes include left ventricular hypertrophy with strain and a QS pattern in lead I along with ST elevation, with reciprocal ST depression in V_6; right ventricular hypertrophy with a QR pattern in lead V_1; ventricular inversion with normal anatomic left ventricular to right ventricular activation occurring in a right-to-left direction, resulting in a narrow Q wave in lead V_1 and an absent Q wave in lead V_6; clockwise rotation of the heart from lung disease or pneumothorax may move the transition leads leftward to lead V_5 or V_6 and therefore lead V_1 may have a QS pattern; hypertrophic cardiomyopathy with asymmetric septal hypertrophy (deep and usually not wide Q waves are found in the lateral leads due to septal hypertrophy.); replacement by nonfunctioning living tissue (myocarditis, progressive muscular dystrophy, Friedreich's ataxia, scleroderma and cardiac tumors); replacement with pros-

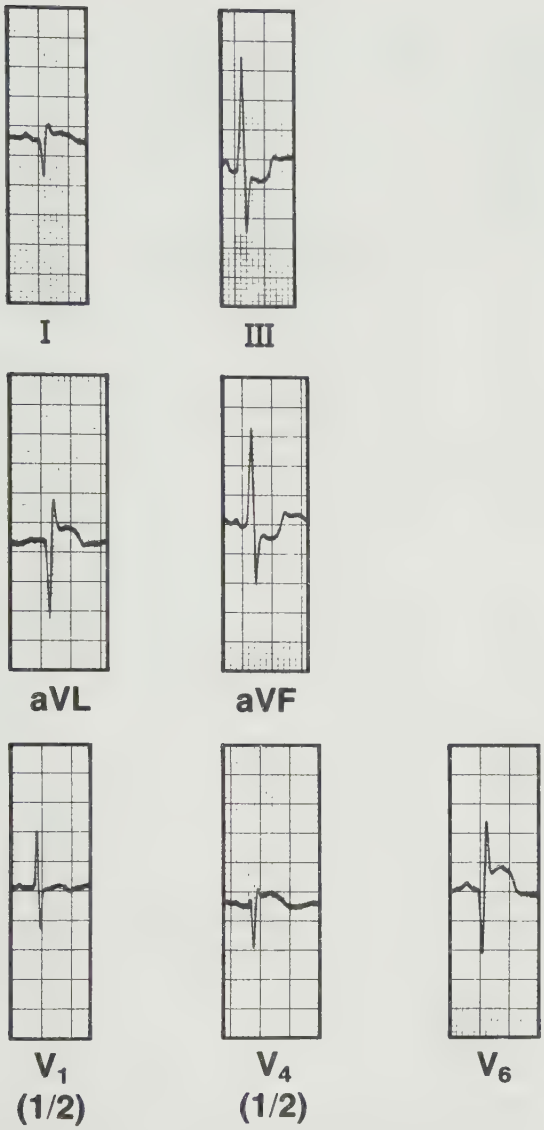


Fig. 45–53. Acute lateral myocardial infarction in a 4-mo-old infant with anomalous left coronary artery originating from the pulmonary artery. The "acute" and "chronic" stages diagrammed in Figure 45–52 occurred simultaneously in this patient. There is both ST elevation and the development of deep, wide Q waves in leads I, aVL, and V_6.

thetic material (when a large prosthetic patch is used on the right ventricular outflow tract, deep, wide Q waves may occur in the anerior chest leads; left bundle branch block, causing a QS pattern in lead V_1; left anterior hemiblock, with Q waves in the lateral precordial leads; Wolff-Parkinson-White syndrome, with wide Q waves in the inferior leads; and intracranial hemorrhage may produce a QS pattern in lead V_1 or V_2.

Body Chemistry

Hyperkalemia

Hyperkalemia is most commonly due to renal failure, salt-losing adrenogenital syndrome, or iatrogenic overdose.[85] The serum potassium level can be predicted from the electrocardiogram because of the different effects on the action potential. At a level of 5.5 to 6.5 mEq/L, the velocity of phase 3 of the action potential increases and the T waves on the electrocardiogram become tall and peaked. This is a poor sign because many normal children have "peaked" T waves and many children with hyperkalemia do not have peaked T waves. At a serum potassium level over 6.6 mEq/L, the cellular resting membrane potential is decreased (more toward 0) and therefore the conduction velocity (and $\dot{V}$ max) is decreased. This causes interventricular conduction delay. This may be manifested as diffuse QRS widening or it may have a specific bundle branch block or fascicular block pattern. These are generally very bizarre QRS complexes and may be combined with ST elevation, leading to the mistaken diagnosis of ventricular tachycardia if preceding P waves are missed (Fig. 45–56). If P waves are seen, these complexes may also be mistaken for acute myocardial infarction or pericarditis. At a level over 7.0 mEq/L, intra-atrial conduction delay becomes manifest with prolongation of the P wave. At a level over 8.5 mEq/L, the P wave may disappear. Direct conduction from the sinus node through atrial Purkinje fibers to the atrioventricular node and the ventricles has been hypothesized. The sinus node and atrial Purkinje fibers are most resistant to hyperkalemia. Since the ordinary atrial muscle fibers are depressed by the hyperkalemia, they neither conduct nor contract. Therefore there may be no P wave despite conduction through the atrium. This has been termed "sinoventricular conduction." At approximately 9.0 mEq/L, arrythmias begin: atrioventricular block, ventricular tachycardia, and ventricular fibrillation.

Hypokalemia

Hypokalemia is most often found with vomiting, diarrhea, endocrine disease (Cushing's disease, hyperaldosteronism, cortisone treatment), acquired renal disease, iatrogenic lack of intake, and most importantly to cardiologists, diuretic treatment. Hypokalemia causes a lengthening of phase 3 of the action potential with a loss of the plateau and a slower descent. At a level of 2.7 to 3.0 mEq/L, the electrocardiograms in 35% of adults have demonstrated abnormalities of hypokalemia and at a level below 2.7 mEq/L, 78% are abnormal.[86] The most prominent changes are the decrease in the T-wave amplitude (occasionally with ST depression) and an increase in the U-wave amplitude. Therefore hypokalemia causes broadened T and U waves with a normal onset to the T wave (Fig. 45–57). Other causes of prominent U waves are bradycardia, ischemia, left ventricular hypertrophy, quinidine, procainamide, phenothiazines, and cerebrovascular accidents. Hypokalemia may cause a minimally prolonged QRS duration. Arrhythmias are rare with hypokalemia unless the patient is receiving digitalis. In this case, hypokalemia enhances the arrhythmogenic effects of digitalis.

Hypercalcemia

Hypercalcemia may be due to hyperparathyroidism, hypophosphatasia, hypervitaminosis D, idiopathic hypercalcemia, or iatrogenic overdose with rapid infusion of calcium. Hypercalcemia shortens phase 2 of the action potential and therefore shortens the Q–T interval by shortening the ST segment. It may be difficult to diagnose hypercalcemia on the electrocardiogram in sinus rhythm, because the Q–T interval may be normal and only the ST segment is shortened. The most common effect of hypercalcemia is on the

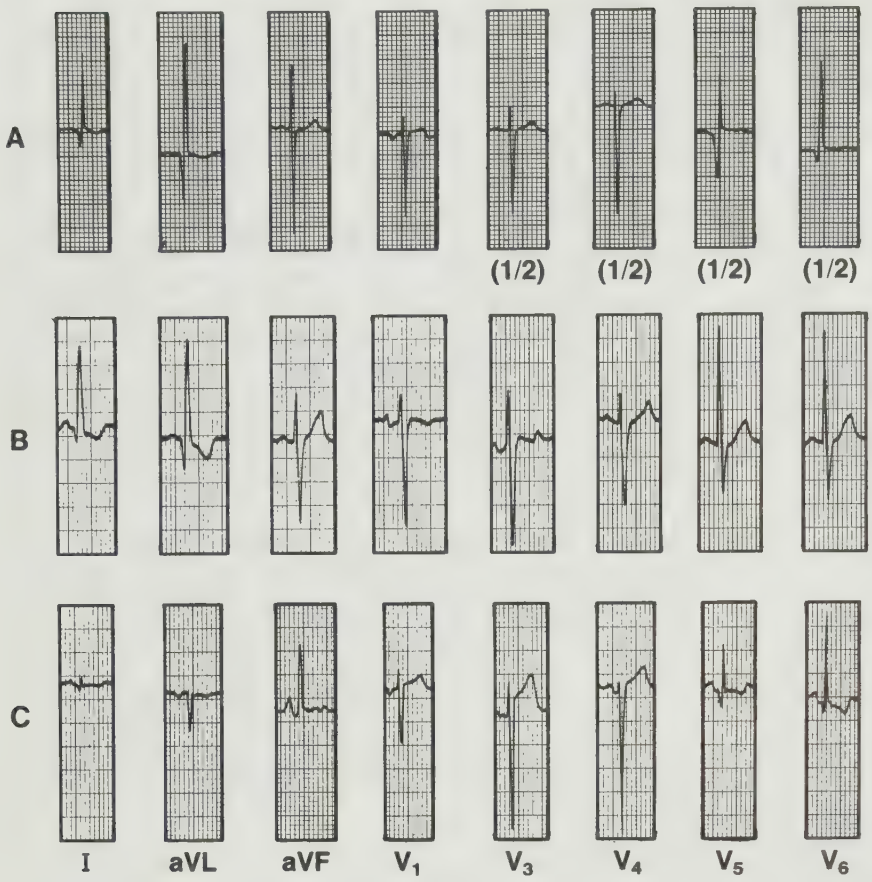


Fig. 45–54. Old myocardial infarction in three children with anomalous left coronary artery originating from the pulmonary artery. (A) The top row of tracings are from a 7-mo-old child. They demonstrate left-axis deviation of the QRS mean vector in the frontal plane, a diminished R wave between lead V_3 and lead V_6, and deep, wide Q waves in leads I, aVL, V_5, and V_6. In the middle row, the tracings are from a 7-yr-old girl. The findings are similar to those in the 7-mo-old, with the exception that there are no Q waves but deep S waves in leads V_5 and V_6. (B) The middle row therefore corresponds more to the "adult" type of electrocardiogram in anomalous left coronary artery. (C) In the bottom tracings, taken from another 7-yr-old, there is no left-axis deviation, but there are deep Q waves in leads aVL, V_5, and V_6. This is more consistent with the "infantile" pattern. This demonstrates that the labels may not be helpful. In all these electrocardiograms there is a loss of R wave in lead V_4, and both Q-wave and T-wave inversion in leads I and aVL.

sinus node, with slowing of the sinus rate, sinoatrial block, or sinus arrest. Atrioventricular block and ventricular arrhythmias are uncommon unless the patient is taking digitalis. In this case, hypercalcemia potentiates digitalis effects and digitalis-induced arrhythmias.

Hypocalcemia

Hypocalcemia can be due to malabsorption, hypoparathyroidism, vitamin D deficiency, stress in the newborn period, or iatrogenic lack of intake. This causes a prolongation of phase 2 of the action potential and prolongation of the ST segment on the electrocardiogram. Therefore hypocalcemia has a different effect from hypokalemia, which prolongs phase 3. In hypokalemia, the onset of the T wave occurs at the normal time, the T-wave duration (including the U wave) is prolonged, and the Q–T (or Q–U) interval is prolonged. In hypocalcemia, the T-wave duration is normal and the Q–T interval is prolonged because there is a prolonged ST segment and a prolonged onset of the T wave (see Fig. 45–20). The interval from the onset of the QRS complex to the onset of the T wave (Q–OT interval) correlates well with serum calcium in newborn babies (see Fig. 45–20). In premature babies, the normal corrected Q–OT (Q–OT/square root of the P–R) is 0.20 or less, and in full-term infants it is 0.19 or less.[16] Using these parameters, if the Q–OTc interval is normal, the serum calcium concentration is normal in 98% of babies; if the Q–OTc interval is prolonged, 70% are hypocalcemic with a total serum calcium concentration less than 7.5 mg/dL. The remainder of the infants with a prolonged Q–OTc interval have undergone severe neonatal stress. Although patients with hypocalcemia have a prolonged Q–T interval, arrhythmias are rare, perhaps because repolarization is uniformly prolonged throughout the ventricles. Atrioventricular block may occasionally occur.

Hypermagnesemia

Hypermagnesemia decreases the upstroke velocity of the action potential and shortens the duration of phase 2 of the action potential, simulating hypercalcemia. Isolated hypermagnesemia produces few changes on the electrocardiogram, although individual cases of prolonged P–R interval and interventricular conduction delay have been reported.[4]

Hypomagnesemia

The effects of hypomagnesemia on the action potential and the electrocardiogram are similar to those of hypokalemia. In newborns, hypomagnesemia may coexist with hypocalcemia. In these infants, the electrocardiographic pattern is similar to combined hypocalcemia and hypokalemia: prolonged plateau and slower descent. These produce a summation of effects to delay repolarization and therefore large U waves are observed with flattened T waves.

Hypernatremia and Hyponatremia

In the tissue bath, the effects of sodium on the action potential are considerable, with an increased sodium concentration causing an increase in the slope of phase 0 (increased $\dot{V}$ max) and prolonged phase 3. A decrease in sodium concentration causes the opposite effect. However, in the range of serum sodium concentrations that

are physiologically possible in the body, these effects are not usually seen on the electrocardiogram. The effects of sodium may be demonstrated in the patient with a prolonged QRS duration due to quinidine or hyperkalemia, where sodium infusion improves interventricular conduction and shortens the QRS duration.

Hypoglycemia

The electrocardiographic changes of hypoglycemia are thought to be caused by the associated hyperkalemia that is frequently present. In hypoglycemia, insulin secretion is inhibited and hyperkalemia may result.

Hypoxia and Acidosis

The effects of the action potential of hypoxia and acidosis are similar to those of increased extracellular potassium and the changes may be due, in part, to leakage of potassium out of the cell.[71] The QRS duration is prolonged, as is the Q–T interval. All types of atrial and ventricular arrhythmias may occur in addition to atrioventricular block.

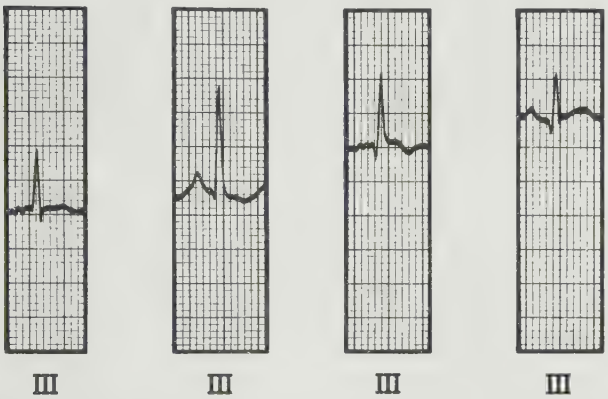


Fig. 45–55. Myocardial infarction in Kawasaki's disease. These tracings are from a 9-yr-old boy who was hospitalized on the seventh day of the illness. The first tracing is from the day of admission. He was asymptomatic at the time. The second tracing was taken 3 days later. Note the development of small Q waves, which were not present previously, and the T-wave inversion in lead III. Four days later, the Q waves have deepened and are now slightly wider. There is also ST elevation with the terminal portion of the T wave inverted. The day after the third tracing, the Q wave remains and the T waves have normalized. By radionuclide imaging, the entire inferior wall of the left ventricle was infarcted. This points out the subtle changes that may occur in an extensive myocardial infarction in a child. While the depth of the Q wave in the last tracing is not distinctly abnormal, the new appearance of the Q wave is abnormal and the width of the Q wave is also abnormal.

Antiarrhythmic Drugs

Digitalis

Digitalis shortens phase 2 of the action potential and also shortens the action-potential duration. The ST–T-wave changes can be explained by the effect of digitalis to hasten repolarization. Digitalis tends to cause all layers of the ventricle to repolarize simultaneously, resulting in greater cancellation of the repolarization vector and flat T waves. With moderate amounts of digitalis effect, primarily the onset of repolarization is affected, as represented in

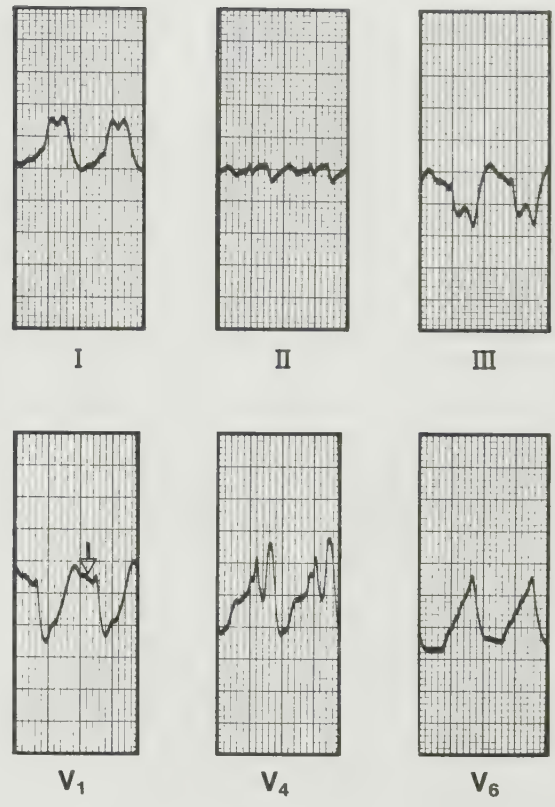


Fig. 45–56. Hyperkalemia. These tracings are from a 2-day-old infant with renal failure and hyperkalemia. The QRS complex is similar to left bundle branch block. The small P waves are marked with an arrow in lead I, indicating that this is sinus rhythm.

the ST segment. The ST segment is depressed most in the leads facing the left ventricle; taller P waves are generally associated with more ST depression.[71] The late part of repolarization is still unaffected. Therefore the terminal parts of the T waves are normal and concordant with the QRS complex, although the overall Q–Tc interval may be shortened (Fig. 45–58A). With increasing amounts of digitalis effect, the entire process of repolarization is reversed (from endocardium to epicardium) and the same leads with ST depression also show T-wave inversion. The T waves are coved and the descending limb of the ST segment and T wave has an angle of 90° wth the ascending limb (Fig. 45–58B).[86]

The effect of digitalis on impulse formation and conduction results from a combination of direct and vagotonic effects. The cellular basis of these effects has been reviewed by Reder and Rosen[87] The overall effect of digitalis is to slow the sinus rate, speed intra-atrial conduction, decrease atrial automaticity, and prolong atrioventricular condition. This may be manifest on the electrocardiogram as sinus bradycardia and a prolonged P–R interval.

Digitalis toxicity results in further slowing of the sinus rate, sinoatrial block, or sinus arrest, and second-degree atrioventricular block (usually type 1, Wenckebach), or third-degree atrioventricular block. These manifestations are more common in children than those that result in increased atrial, junctional, or ventricular automaticity; namely, premature atrial contractions, supraventricular tachycardia, nonparoxysmal junctional tachycardia, premature ventricular contractions, or ventricular tachycardia.[88,89] If atri-

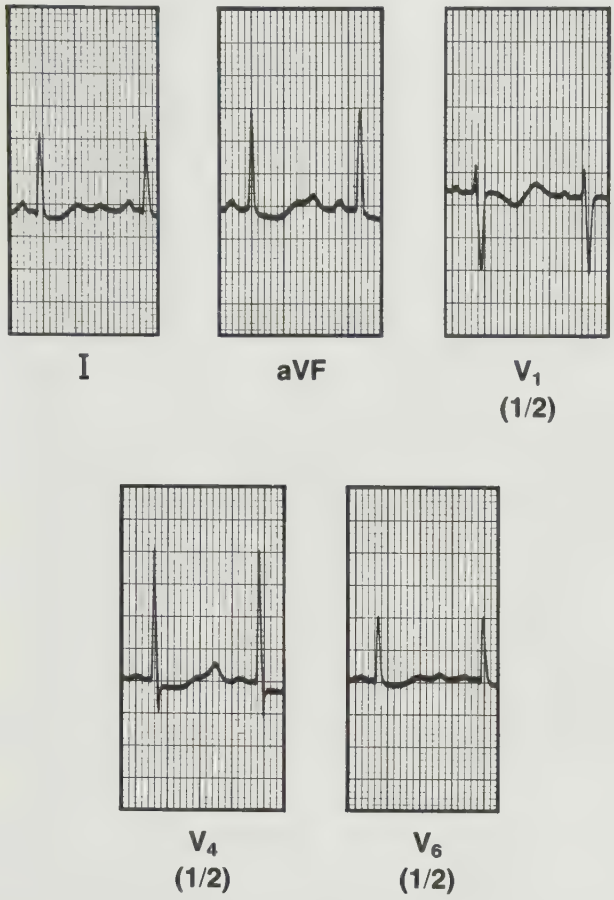


Fig. 45–57. Hypokalemia. These tracings are from a 4-yr-old with the nephrotic syndrome. Note the prominent U waves in all leads with ST depression and T-wave inversion in leads I, aVF, V_4, and V_6.

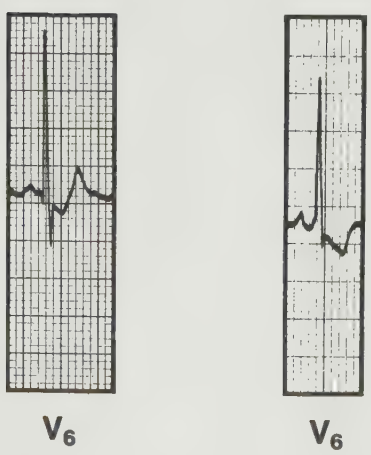


Fig. 45–58. Digitalis effect. (A) ST depression with normal terminal portion of the T wave. (B) Coved initial portion, with complete inversion of the T wave.

oventricular block and premature ventricular contractions occur on the same electrocardiogram, digitalis toxicity should be suspected. Digitalis toxicity (especially associated with hypokalemia) has been associated with "bidirectional tachycardia." This has the morphology of constant complete right bundle branch block with alternating right-axis deviation and left-axis deviation (Fig. 45–59). Bidirectional tachycardia is probably ventricular tachycardia with alternating exit pathways, rather than junctional tachycardia with alternating bundle branch block.[91]

Quinidine, Procainamide, and Disopyramide

These drugs are class IA antiarrhythmic agents and have similar actions. Quinidine's effects will be used as examples of the other type IA agents. Quinidine decreases the upstroke velocity (reduced $\dot{V}$ max) of all action potentials, prolongs phase 3 (resulting in a prolonged action-potential duration), and reduces automaticity. The decreased upstroke velocity results in interventricular conduction delay and a prolonged QRS duration. This may result in a diffusely widened QRS or a specific right or left bundle branch block pattern. The effects on the T waves are both "secondary" (to the interventricular conduction delay) and "primary" (due to prolongation of the action potential). Since the terminal part of repolarization is most affected, the early part of the T wave may have decreased amplitude and the terminal part may be increased. This is difficult to distinguish from a U wave. The Q–T (or Q–U)

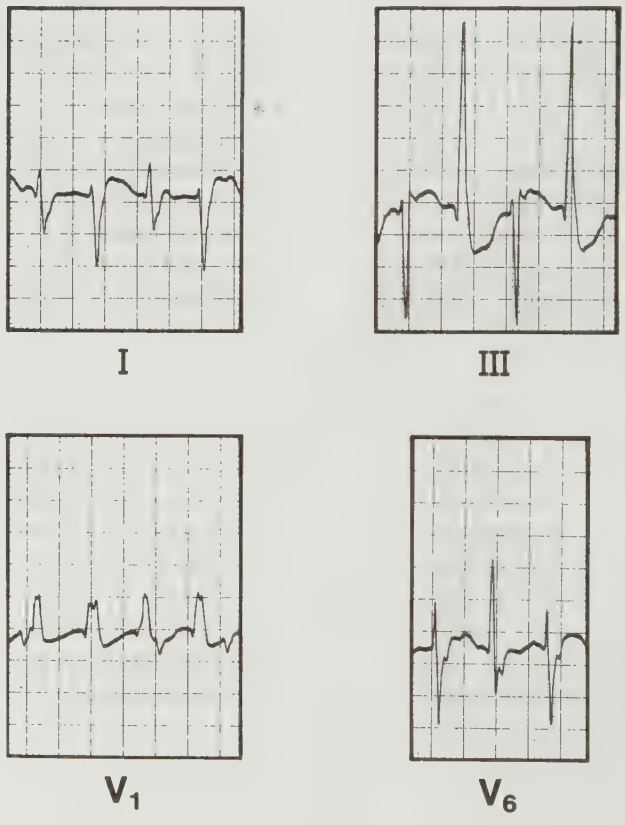


Fig. 45–59. Bidirectional tachycardia. This was due to digitalis intoxication and hypokalemia in a 5-yr-old child. There is constant right bundle branch block in lead V_1 with alternating right-axis and left-axis deviation shown in the limb leads.

interval is prolonged. Because of its vagolytic properties, quinidine may shorten the P–R interval slightly.

Quinidine toxicity is manifest on the electrocardiogram as a decreased atrial rate usually due to sinoatrial exit block; prolongation of the P-wave duration due to intra-atrial conduction delay; prolongation of the P–R interval due to prolongation of His–Purkinje conduction; prolongation of the QRS complex to 125% or more of the original QRS duration (Fig. 45–60); further prolongation of the Q–T interval due to an increase in refractory period dispersion throughout the ventricles;[91] and premature ventricular contractions and ventricular tachycardia.[92] The ventricular tachycardia in quinidine toxicity may have a similar morphology to that sometimes found in other patients with prolonged Q–T intervals and is called torsades de pointes (Fig. 45–61).[93]

Lidocaine, Phenytoin, Mexiletine, and Tocainide

These drugs increase the slope of phase 0 (increase $\dot{V}$ max) in diseased tissue (improving conduction) and shorten action-potential duration, but have very little effect on the surface electrocardiogram.[94] Rarely, with high doses of phenytoin the P–R and Q–T intervals may shorten due to accelerated atrioventricular conduction and shortened ventricular refractoriness. If phenytoin is given to a patient with a prolonged Q–T interval for prevention of ventricular tachycardia, effective antiarrhythmic treatment may occur without shortening the Q–T interval.[95]

Propranolol

Propranolol decreases the upstroke velocity of phase 0 (reduces $\dot{V}$ max), shortens the action-potential duration, and decreases automaticity. In the patient, propranolol's effects are mainly antiadrenergic. The sinus rate is slowed, the P–R interval is prolonged and the Q–T interval may be shortened. Similar to phenytoin, propranolol may not shorten the Q–T interval in a patient with a prolonged Q–T interval but it may be effective in preventing ventricular tachycardia and sudden death.[95]

Verapamil

Verapamil is a calcium antagonist with primary effects on the sinus node and atrioventricular node. It decreases the slope of phase 0 (reduced $\dot{V}$ max), prolongs the action potential duration and reduces automaticity. The electrocardiographic findings are a slowed sinus rate and prolonged P–R interval.

Amiodarone

Amiodarone is primarily a Class III agent that prolongs action-potential duration; it also has some Na-channel blocking activity to decrease $\dot{V}$ max; it also possesses beta-blocking and calcium-blocking activity. Amiodarone virtually always prolongs the Q–T interval and decreases the heart rate. There is less constant P–R and QRS prolongation.[96]

Encainide and Flecainide

These are both Class Ic agents with profound Na-channel blocking activity, therefore markedly decreasing $\dot{V}$ max. This has the effect of prolonging the QRS complex at effective, rather than toxic, doses. It is usual for children on encainide to have QRS prolongation of 50% over base line.[97] Flecainide causes less QRS prolongation. In patients receiving both of these drugs, the measured Q–T interval increases due to the QRS prolongation; repolarization (the interval from the end of the QRS complex to the end of the T wave, the so-called J–T interval) does not prolong.

Anesthetic Agents

Halothane decreases the action potential duration slightly by increasing the slope of phase 2 and phase 3. These effects are rarely seen on the electrocardiogram, but occasionally the Q–T interval is shortened and there may be a decrease in T-wave amplitude. Halothane sensitizes the heart both to vagal and sympathetic stimulation. Therefore bradycardia and ventricular arrhythmias may occur. Methoxyflurane, teflurane, and enflurane have similar effects on the electrocardiogram to those of halothane.

Chloroform, ethyl chloride (given by inhalation), trichloroethylene, and cyclopropane all may cause ventricular arrhythmias. Diethyl ether and other ethers have no effect on the electrocardiogram.[98]

Psychotropic Drugs

Phenothiazines cause shift of potassium inside the cell, thus decreasing the extracellular potassium and therefore prolonging phase 3 of the action potential.[99] These changes are similar to those found with quinidine: The T waves have reduced amplitude with prominent terminal depolarizations. It is difficult to distinguish a U wave from broad notched T waves with an increased terminal component. The Q–T (or Q–U) interval is prolonged.[100] In therapeutic doses, arrhythmias are rarely observed with phenothiazines, but in overdosage, ventricular arrhythmias may occur.

The electrocardiographic changes with tricyclic antidepressants

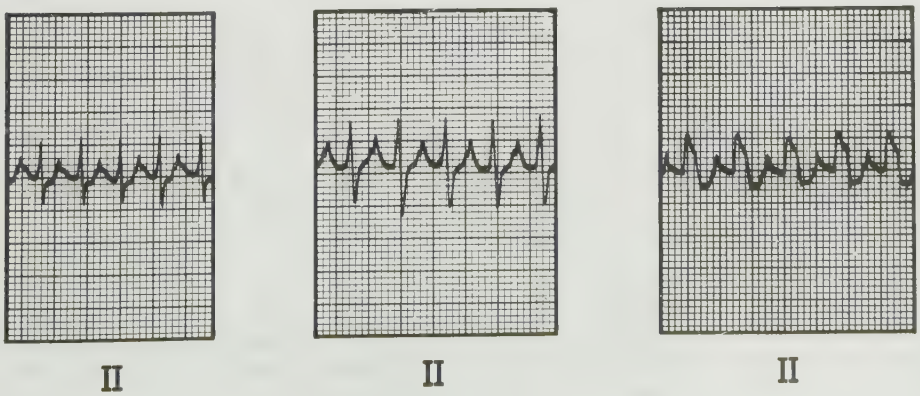


Fig. 45–60. Procainamide effect and toxicity. (A) Before medication, this 5-mo-old girl had supraventricular tachycardia due to an atrial ectopic focus at a rate of 270 beats/min. The QRS duration was 0.05 sec. (B) After 70 mg of procainamide, the rate slowed to 225 beats/min and the QRS duration increased to 0.08 sec. (C) After 80 mg of procainamide, the rate did not change, but the QRS duration increased to 0.10 sec with a pattern of left bundle branch block.

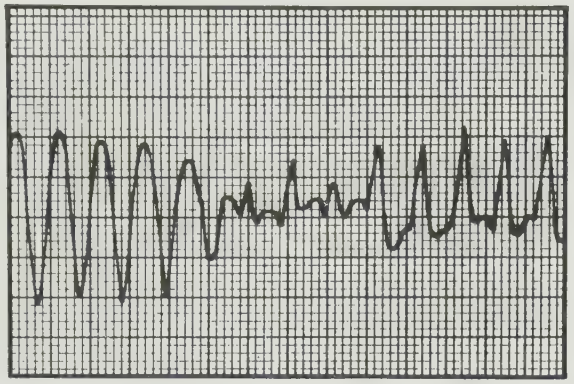


Fig. 45–61. Torsades de pointes due to quinidine toxicity. There are two different polarities to the tachycardia separated by a narrower-transition QRS.

occur in 20% of adult patients taking the drugs. The most common manifestations are sinus tachycardia, prolonged P–R interval, and flat T waves. Less commonly observed are QRS prolongation, Q–T interval prolongation, and ST–T-wave changes. Overdosage with tricyclic antidepressants may cause atrial or ventricular arrhythmias or atrioventricular block.[8]

Imipramine (Tofranil) causes an imbalance of intracellular and extracellular potassium with an increase in serum potassium. In one reported case of an overdosage in a child, atrial flutter, atrioventricular block, interventricular conduction delay, and ventricular tachycardia were observed in the same patient.[101]

Central Nervous System Effects

Congenital Prolongation of the Q–T Interval

Jervell and Lange-Nielsen[13] and Romano[102] and Ward[103] described syndromes that have in common congenital prolongation of the Q–T interval. syncope or sudden death, and hereditary transmission. In the Jervell–Lange-Nielsen syndrome, the hearing is abnormal and the heredity is autosomal recessive; in the Romano–Ward syndrome, the hearing is normal and the heredity is autosomal dominant. The electrocardiograms are similar. The T waves may be inverted, biphasic, and vary in both shape and amplitude from minute to minute. The T waves frequently have bizarre shapes with greater amplitude at the terminal portion of the T wave (Fig. 46–62).

Although the exact mechanism of the prolonged Q–T interval is uncertain, central and peripheral nervous system sympathetic imbalance is involved. Normally, innervation to the heart is asymmetric: Fibers project from the right hypothalamus to the right stellate ganglion and supply the anterior surface of the cardiac ventricles; fibers from the left hypothalamus project to the left stellate ganglion and supply the left lateral and posterior wall of the cardiac ventricles. Experimental stimulation of the left stellate ganglion prolongs the Q–T interval and causes ST depression.[71] In patients with a congenitally prolonged Q–T interval, left stellate ganglionectomy may shorten the Q–T interval and eliminate episodes of syncope, adding strength to the hypothesis of neural imbalance as a cause of this syndrome.

Central Nervous System Injury

In children with moderate to severe head trauma or in those who have undergone neurosurgical procedures, the electrocardiogram has been reported to be abnormal in 75%.[104] The most common abnormalities are a prolonged Q–T interval with either notched, bizarre-shaped T waves or prominent U waves. Occasionally, the T waves are diffusely flattened in the lateral leads or even inverted with ST depression.[105] ST elevation is rare in central nervous system lesions but has been reported.[106] Occasionally, J or Osborne waves are found (see section on "Hypothermia"). These repolarization changes are thought not to be due to increased intracranial pressure but rather to differential stimulation or suppression of the cortical representations of the sympathetic fibers. In some patients with central nervous system lesions, there is evidence at autopsy for cardiac abnormalities, primarily subendocardial ischemia. Identical lesions can be produced by catecholamine infusion.[107]

Arrhythmias can occur with central nervous system injury. Vagal tone is enhanced and there may be alternating sympathetic stimulation. The bradyarrhythmias (sinus bradycardia, wandering atrial pacemaker, junctional rhythm, and type 1 second-degree atrioventricular block) generally respond to atropine, supporting the theory of their central vagal origin. Sinus tachycardia may occur in addition to any of the pathologic tachyarrhythmias.

Hypothermia

A J wave (or Osborne wave) occurs on the electrocardiogram of patients with a body temperature below 25°C. This is a slowly inscribed extra deflection between the QRS and the early ST segment (Fig. 45–63).[108] The P–R and Q–T intervals prolong and there may be ST depression or ST elevation. Initially, the sinus node slows but at approximately 29°, 50 to 60% of adult patients with hypothermia have atrial fibrillation.

Neuromuscular Disorders

The electrocardiogram in Duchenne's progressive muscular dystrophy is abnormal in about 75% of patients. The abnormalities are most specific to Duchenne's dystrophy and occur less frequently in the other forms of muscular dystrophy.[109] The usual findings are tall R waves in the right precordial leads (with or without interventricular conduction delay) and deep narrow Q waves in the left precordial leads. These changes are thought to be due to selective scarring of the posterobasal left ventricle, rather than right ventricular hypertrophy, pulmonary hypertension, or septal hypertrophy.[110] The scarring could be due to continued stress on the left atrioventricular ring due to poor support of the mitral valve from abnormal cardiac muscle. These electrocardiographic changes do not correlate with the degree of involvement in the skeletal muscles or the degree of cardiomyopathy. Late in the disease, when cardiomyopathy is present, any type of active arrhythmias may occur: sinus tachycardia, premature atrial contractions, atrial flutter, premature ventricular contractions, or ventricular tachycardia.

In Friedreich's ataxia, the electrocardiogram is abnormal in 90% of the patients, most commonly QRST discordance; 20% have asymmetric septal hypertrophy as the cause of deep Q waves in the lateral precordial leads.[8] Either left ventricular hypertrophy or right ventricular hypertrophy may also occur. The arrhythmias are similar to those in muscular dystrophy.

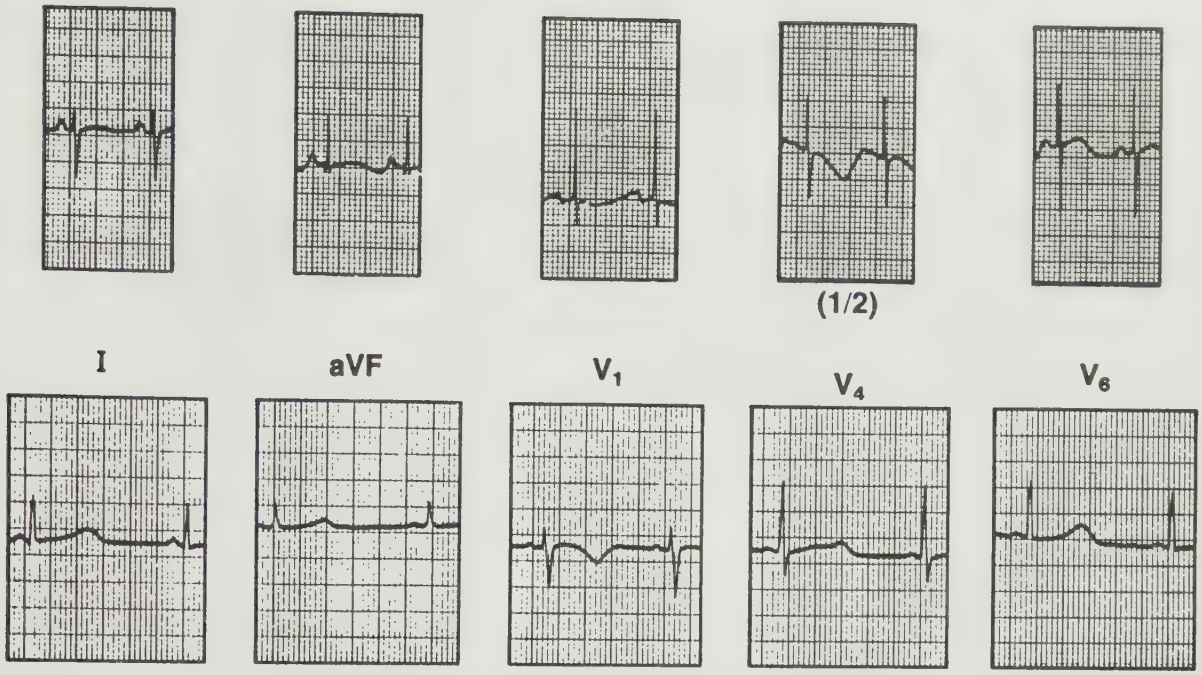


Fig. 45–62. Congenital prolongation of the Q–T interval. Top tracings from a 9-day-old infant with a history of ventricular tachycardia and ventricular fibrillation at the age of 4 days. All the T waves are abnormal, however, the T waves in lead V_4 (at half standard) are especially bizarre. Bottom tracings from a 12-yr-old child who had his first episode of syncope at the age of 10 yr. He was being treated for a familial seizure disorder. Note that the terminal portion of the T wave in lead V_4 is greater in amplitude than the initial portion.

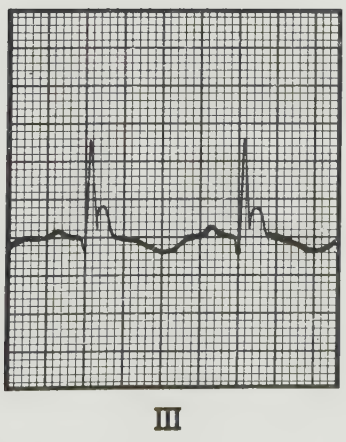
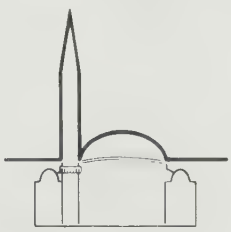


Fig. 45–63. Hypothermia. This tracing was taken from a 3-mo-old with hypothermia and severe brain damage. The J wave is the rounded, second portion of the QRS complex. The heart rate is slow for an infant of this age. The P–R interval, QRS duration, and Q–T interval are also prolonged.



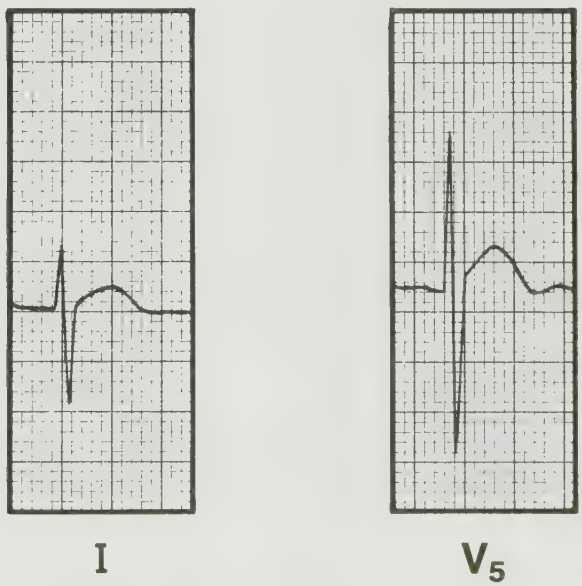


Fig. 45–64. Hypothyroidism. The "mosque" sign is demonstrated with an absence of the ST segment and a symmetrically rounded T wave.

The electrocardiogram in myotonic dystrophy is abnormal in about half of the patients, with low-voltage P waves, prolonged P–R interval, left-axis deviation, left bundle branch block, and ST–T-waves changes. Atrial fibrillation is common.

Connective-Tissue Disease

In patients with scleroderma or systemic lupus erythematosus, pulmonary hypertension may cause right ventricular hypertrophy and systemic hypertension may cause left ventricular hypertrophy. In addition, ST elevation and T-wave changes may occur as a result of pericarditis. Chronic pericarditis with fibrin insulation or diffuse myocardial fibrosis may lead to low-voltage QRS complexes. Supraventricular tachycardia, ventricular tachycardia, atrioventricular block, and bundle branch block are common in later stages of these diseases.

Metabolic Diseases

Hypothyroidism

The classic sign of hypothyroidism is the ''mosque'' sign (appropriately, originally described in Turkey by Ertugrul in 1966):[111] A dome-shaped symmetric T wave with an absent ST segment (Fig. 45–64). This was present in 37% of children with hypothyroidism. Therefore, if present, the mosque sign is helpful in the diagnosis; if it is absent, the patient still may have hypothyroidism. Low voltage of the P waves, QRS complexes, and T waves is also common, and most likely due to myocardial edema, rather than myxomatous pericarditis, which is exceedingly rare.[112] Sinus bradycardia occurs in children with hypothyroidism, usually after 3 yr of age.

Hyperthyroidism

The majority of children with hyperthyroidism have sinus tachycardia, and approximately 50% have left ventricular hypertrophy.[113] Less commonly observed are prolonged P–R interval, nonspecific ST–T-wave changes and right bundle branch block. These changes may take up to a year to reverse after the patient becomes euthyroid.

Adrenal Insufficiency

Patients with adrenal insufficiency may have Q–T interval prolongation with inverted T waves. These changes can be reproduced in adrenalectomized animals, but when the hearts are removed from the body, the cardiac action potentials are normal.[87] These changes are therefore thought to be due to autonomic imbalance.

Pheochromocytoma

Excess catecholamines are responsible for the prolonged Q–T interval and T-wave inversion occasionally encountered in patients with pheochromocytoma.

Miscellaneous Diseases

Peritoneal Inflammation

Peritonitis, appendicitis, and ileus may be associated with nonspecific ST–T-wave changes. These are thought to be due to vagally mediated reflexes.[87]

Sarcoid

The granulomas of sarcoidosis have a predilection for the conduction system. The most common lesions are complete atrioventricular block and right bundle branch block. Premature atrial contractions and premature ventricular contractions also occur.[8]

ARTIFACTS

Recognition of artifacts is both important and satisfying: An exercise in mind over matter. Causes of artifacts can be classified into seven major categories as described below.[114]

Causes of Artifacts

Incorrect Positioning of the Electrocardiogram Leads

The most common cause is reversing the right arm with the left arm or the right leg with the left leg. Only the limb leads on the electrocardiographic tracing are affected. If the arm leads are reversed, the P wave, QRS complex, and T wave are inverted in lead I. This can be checked by examining lead V_6, since V_6 has approximately the same vector as lead I. If the complexes in lead I and V_6 are completely different and the P waves are inverted in lead I, the limb leads are reversed (Fig. 45–65 first and second column). If the right leg and the left leg leads are switched, there is practically no change in the electrocardiogram (Fig. 45–65 third column). If the right leg and the right arm leads are switched, lead II is entirely isoelectric. Secondly, the complexes in aVR and aVF are completely positive. It is not possible to calculate a mean vector that is entirely positive in leads aVR and aVF at the same time. Finally, lead I is entirely different from lead V_6. These leads should record similar complexes (Fig. 45–65 fourth column). If the left leg and left arm leads are switched, unlike the other errors, the resultant electrocardiogram is not obviously faulty. This error in position results in abnormal left-axis deviation (Fig. 45–65 fifth column).

The chest leads may be positioned in an incorrect interspace (Fig. 45–66). If all the leads are placed one interspace too high (i.e., third instead of fourth interspace), the R waves are diminished and the S waves are augmented in leads V_4 to V_7. If the leads are placed one interspace too low, the R waves are augmented and the S waves are diminished.

If electrode paste is not cleaned between chest lead placement, the entire anterior chest will become a conductor and the same ''average'' QRS complex will be recorded from each lead. This is a common problem in infants. This should be suspected if every chest lead appears similar (Fig. 45–67).

Patient-Initiated Movement

Hiccoughs. These are monophasic or biphasic deflections that occur randomly throughout the cardiac cycle. They are usually midway in size between a P wave and QRS complex. There is no alteration in the basic rhythm (Fig. 45–68).

Purposeful Movement. Any random depolarization on the electrocardiogram that does not affect the basic rhythm should be suspected as an artifact. If the movement is repetitive (e.g., waving of the hand) it may simulate ventricular tachycardia.

Nonpurposeful Movement. Convulsions, ''jittery'' newborns, and somatic tremors may simulate tachyarrhythmias (Fig. 45–69).

Respirations. The size of the QRS complex may change with normal deep inspiration (Fig. 45–70).

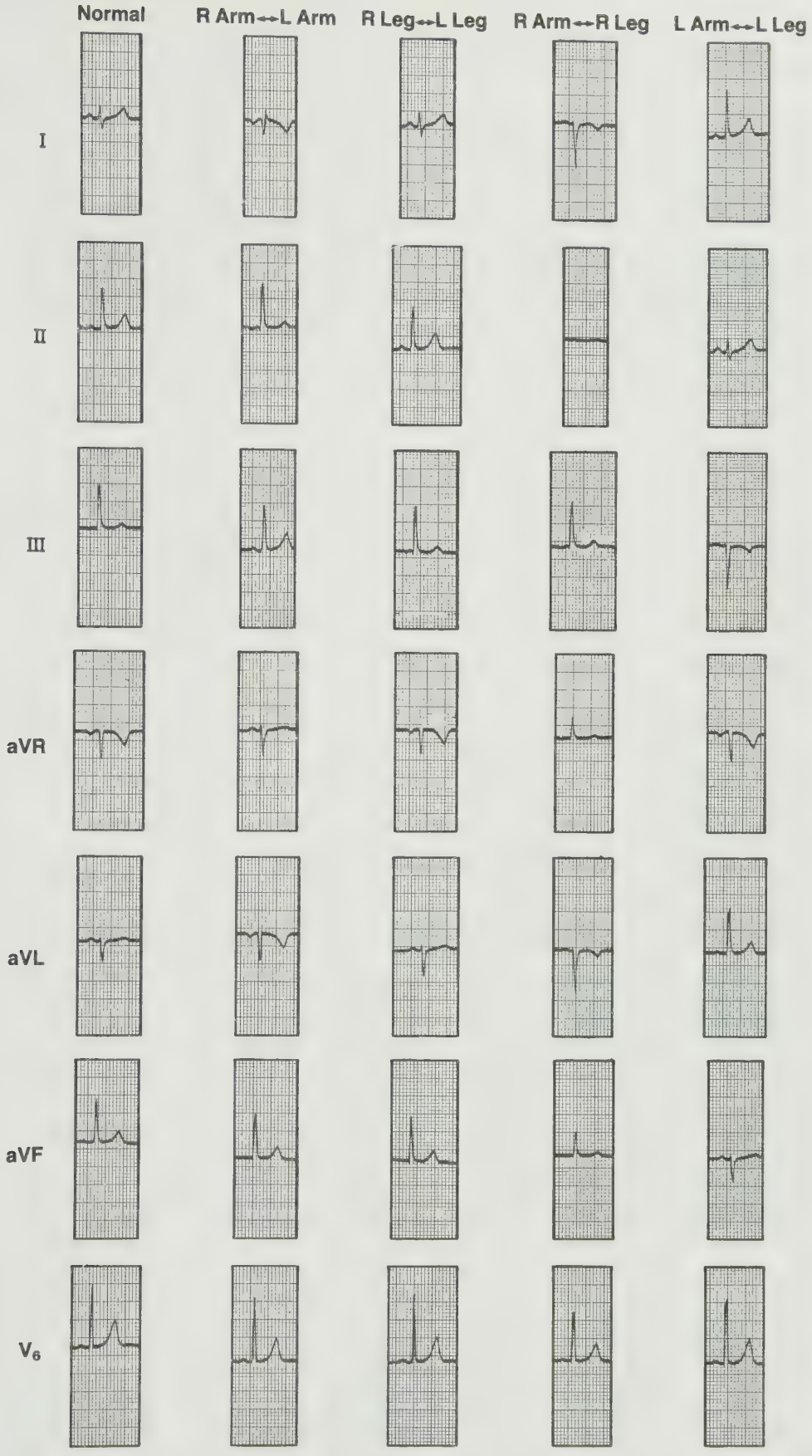


Fig. 45–65. Artifacts due to incorrect limb lead placement. The first column is with the limb leads in the normal positions; the second column is with the right arm and the left arm reversed; the third column is with the right leg and left leg reversed; the fourth column is with the right arm and right leg reversed; and the fifth column is with the left arm and left leg reversed.

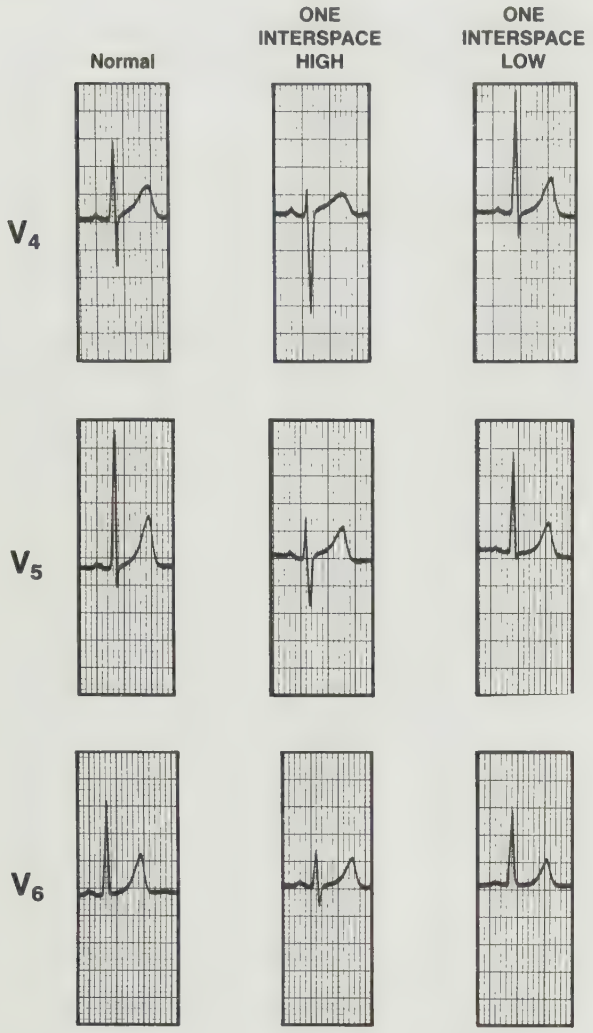


Fig. 45–66. Artifacts due to incorrect precordial lead placement. The first column is with the leads in the normal position. The second column is with the leads placed one interspace too high and the third column is with the leads placed one interspace too low.

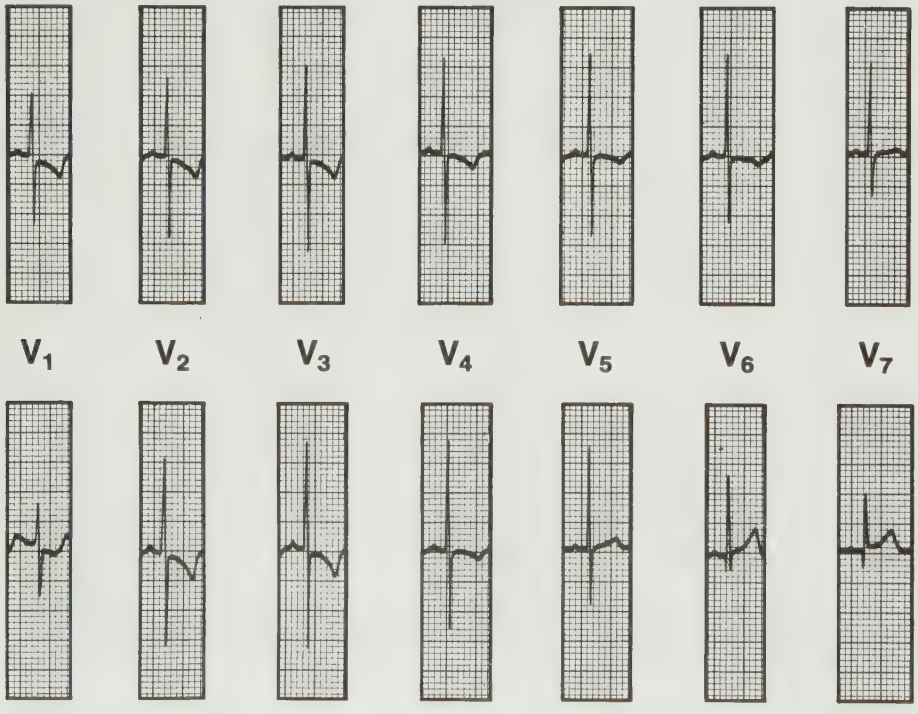
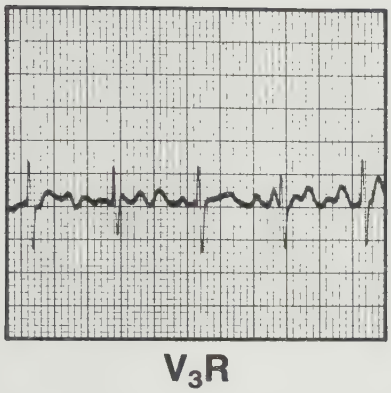


Fig. 45–67. Electrode paste not properly removed between applications of the chest electrodes. Top row with paste smeared on the anterior chest wall causing all complexes to appear the same. Bottom row with proper application of the paste showing a difference between complexes.

Fig. 45–68. Hiccough. The artifact can be best described as being midway in size between a P wave and a QRS complex. It is too large for a P wave. If it were a QRS complex, it should be followed by a T wave.



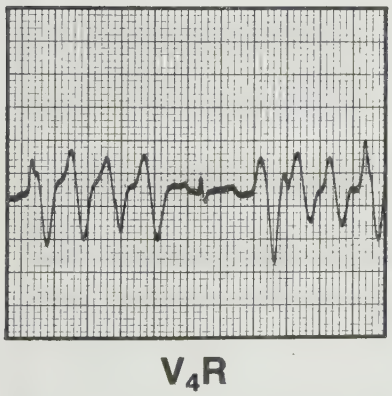
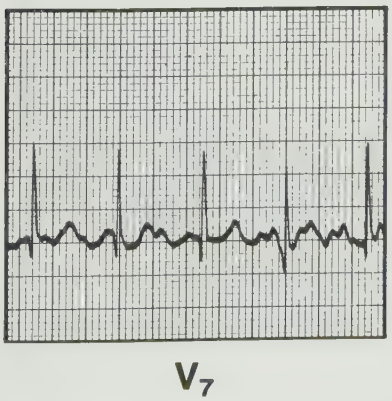


Fig. 45–69. Simultaneous tracings taken during a seizure. In lead V_4R, the tracing appears to be ventricular tachycardia but in the other two tracings, it is apparent that this is artifact and that there is a regular supraventricular rhythm at a rate of 120 beats/min. This demonstrates the value of having three simultaneous leads to aid in the identification of artifacts.



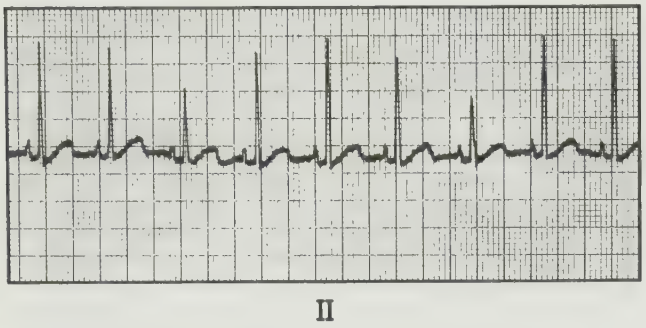


Fig. 45–70 Respiration. The QRS amplitude changes cyclically with approximately 2 sec between the smallest QRS complexes. This corresponds to a respiratory rate of 30 breaths/min.

Therapeutic Manipulation of the Patient

Chest percussion can occur at a rate of approximately 5/sec, which results in an artifact at a rate of 300 beats/min (Fig. 45–71). Open or closed chest massage adds artifactual complexes with each depression of the chest.

Properly Functioning Electrocardiographic System with "Built-in" Artifact

In certain electrocardiographic recording machines, the calibration signal is provided automatically without stopping the paper. Thus the calibration spike may be confused with parts of the true electrocardiogram and form an artifact (Fig. 45–72).

Malfunctioning Electrocardiographic System

Loss of electrode contact is usually marked by an abrupt change in the base line with an absence of cardiac depolarizations. In true asystole the base line usually does not change (Fig. 45–73).

Faulty cable shielding can cause movement artifact on the electrocardiogram.

A repetitive artifact may be produced as a result of faulty cable attachment due to low-amplitude vibration in the environment (Fig. 45–74).

Interference from 60-cycle leakage may result in artifact.

Faulty paper drive—uneven stylus marks may be present, causing the paper to appear "burned." As the paper speed varies, all parts of the P wave, QRS complex, and T wave shorten and prolong with the apparent increase or decrease in heart rate, respectively (Fig. 45–75). At the slowest abnormal paper speeds, the heart rate may appear to be faster than physiologically possible, giving a hint that this may be an artifact (Fig. 45–76).

Faulty stylus—an arc rather than a straight line is drawn for the R wave.

Incorrect stylus position or improper gain—the "isoelectric" line may be unusually flat, indicating that the stylus is at the limit of its excursion or "pegged" (Fig. 45–77A). This can be suspected by the lack of any deflection on one side of the isoelectric line, or a heavy mark at the peak of the QRS complex (Fig. 45–77B).

Current Produced from External Sources

Overhead Warmer or Respirator. Either may cause cyclic production of 60-cycle current, which may be printed on the electrocardiogram. The source of the current or electrical interference may not be identified.

The Infusion-Pump Artifact. This was originally described as a biphasic spike of 30-msec duration with a repetitive rate of 135 beats/min.[115] This artifact is similar to, but wider than, a normal bipolar cardiac pacemaker artifact. The control plunger in a defective infusion pump was the source of current leak, which was transmitted via the intravenous tubing and scalp vein to the patient and detected on the electrocardiogram. We have recently found an artifact that even more closely resembled P waves. This was again due to current leakage from an infusion pump down a nasogastric tube, through the patient and recorded on the electrocardiogram at a rate of 56/min. (Fig. 45–78).

Systematic Approach for the Recognition of Artifacts

A systematic approach is necessary for the recognition of artifacts. The following eight points are helpful in their identification.

1. The shape, amplitude or duration of the wave is atypical for a P wave or a QRS complex. The normal limits for P waves and QRS complexes are defined in the section on "The Normal Electrocardiogram." For example, many ar-

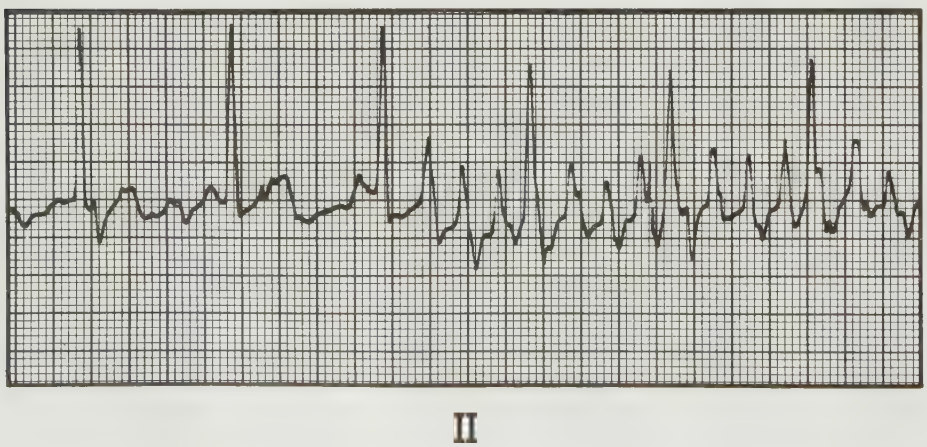


Fig. 45–71. Chest percussion. This is recorded from a 24-hr electrocardiogram and the artifact occurs at a rate of approximately 300 beats/min. Note that the P–R interval is unchanged before and during the artifact.

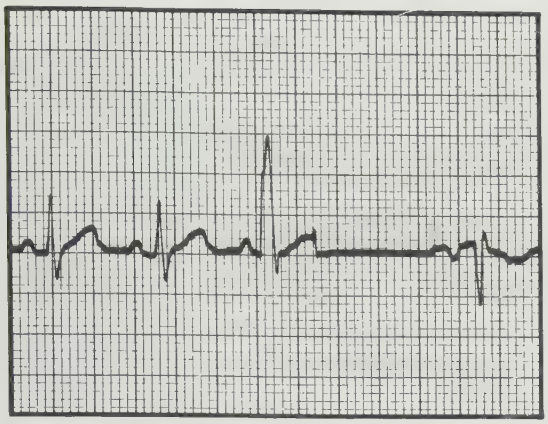
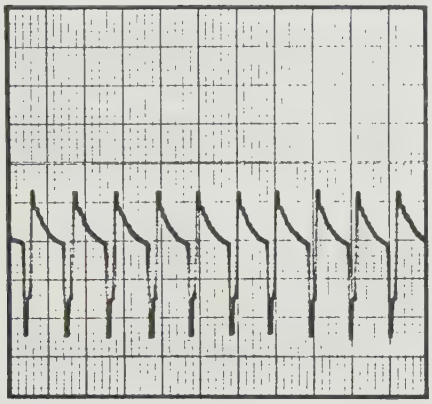


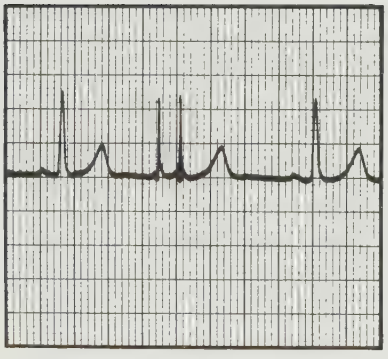
Fig. 45–72. Calibration fusion. These leads were recorded simultaneously. Most apparent in lead II is the onset of a normal QRS complex and then a further spike is introduced on top of the QRS complex. This is followed by an isoelectric segment when the electrocardiograph is not recording. This simulates a premature ventricular contraction.

Fig. 45–73. Asystole versus loss of electrode contact. In the top tracing, there is asystole and in the bottom tracing, there is loss of electrode contact. Note the change in the base line with the loss of electrode contact.



II

Fig. 45–74. Faulty cable attachment. This artifact was eliminated when the connector between the patient cable and the electrocardiograph was secured. This presumably resulted from repetitive vibrations in the pins, which were placed loosely in the slots of the connector.



II

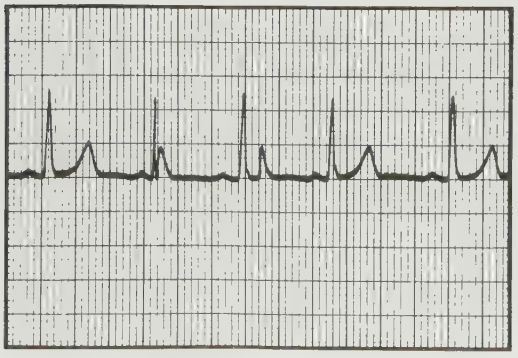


Fig. 45–75. Paper drag due to faulty paper drive. In the top tracing, the middle two QRS complexes are too narrow as compared with the others and indicate that the paper is dragging. Also, there is an uneven stylus mark causing the paper to appear burned in the third complex. In the bottom tracing, in the middle three complexes, the P–R, QRS, and Q–T intervals are all shortened to variable degrees.

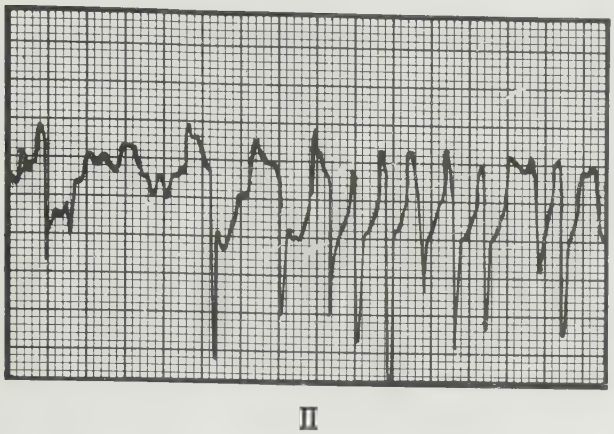


Fig. 45–76. Tape drag causing rapid and irregular rate. In this tracing from a 24-hr electrocardiogram, the rhythm is artifactually irregular, and the rate of 428 beats/min is not physiologic for a 14-yr-old.

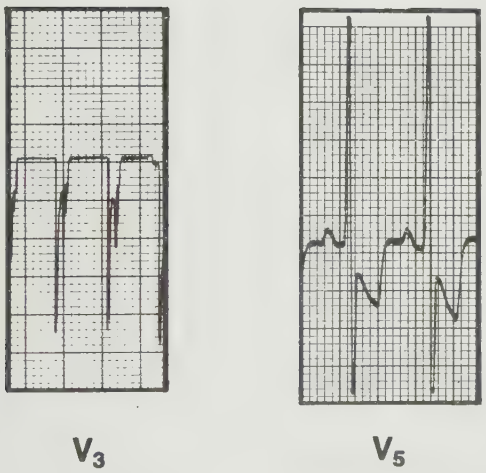


Fig. 45–77. Improper stylus position. In the tracing on the left, the isoelectric line is unusually flat and there are no complexes above this line. This indicates that the upper limit for the stylus was being reached at this point. The patient had ventricular tachycardia. In the tracing on the right, an improper gain setting has been applied such that the QRS complex is clipped at both the top and the bottom of the tracing. In cases such as these, it is impossible to tell how much larger the QRS complex would have been without changing the gain setting.

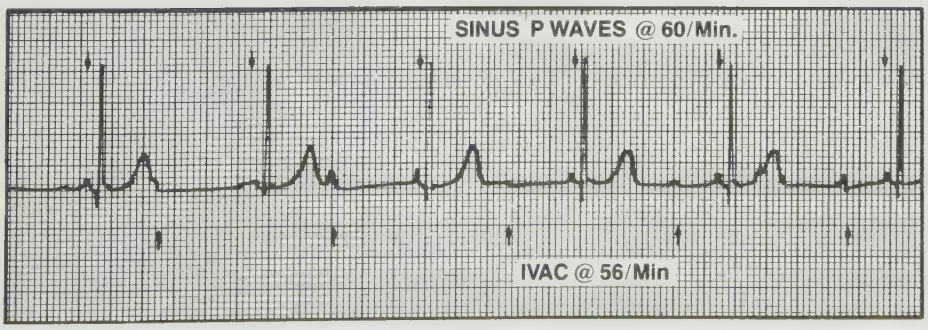
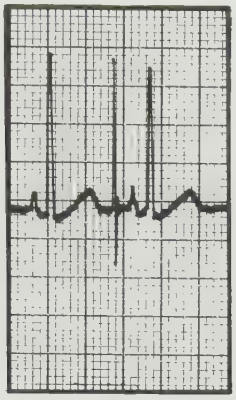


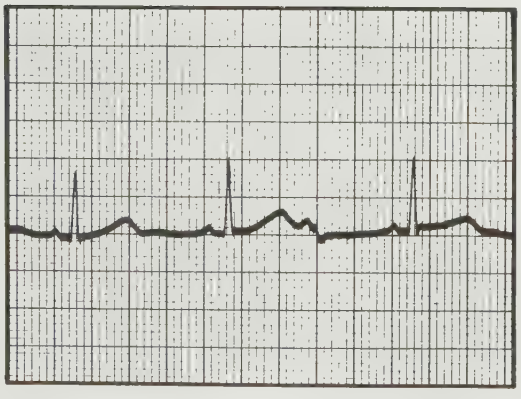
Fig. 45–78. The infusion-pump artifact. The arrows on top of the tracing demonstrate the sinus P waves occurring at a rate of 60/min. The arrows on the bottom of the tracing indicate an artifact occurring at a constant rate of 56/min, which is due to current leak from an improperly shielded infusion pump.



II

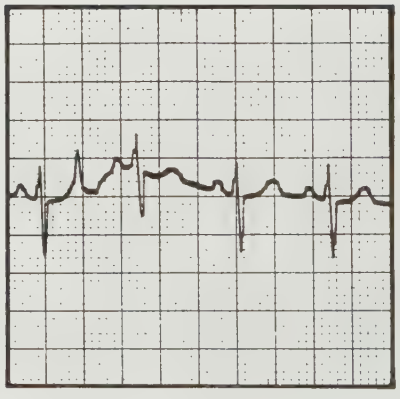
II

Fig. 45–79. Improper duration for QRS complex. Top tracing: The artifact between the two QRS complexes is too narrow to be a QRS complex and it is also not followed by a T wave. Bottom tracing: The artifact in the middle of the tracing is too wide to be a premature ventricular contraction in a 1-mo-old child. It is also accompanied by a base-line shift.



I

Fig. 45–80. This artifact has the appearance of a QRS complex but is not followed by a T wave.



III

Fig. 45–81. Base-line shift. This hiccough is suspected as an artifact because it is too large for a P wave, is not followed by a T wave, and results in a base-line shift.

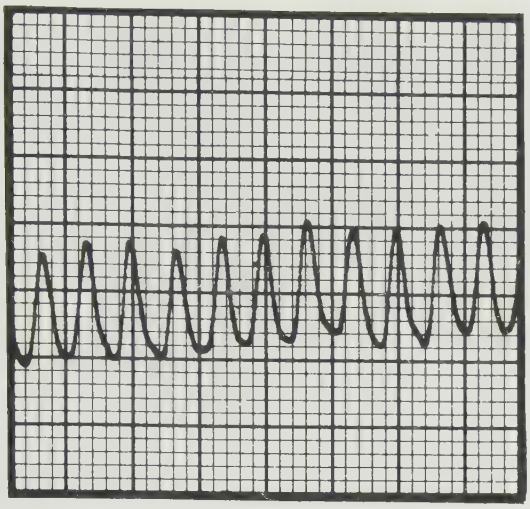


Fig. 45–82. Unphysiologically rapid rate. This tracing was recorded on a 24-hr electrocardiogram from a 6-yr-old child. While these artifacts may appear similar to QRS complexes, the rate of 480/min is not physiologic.

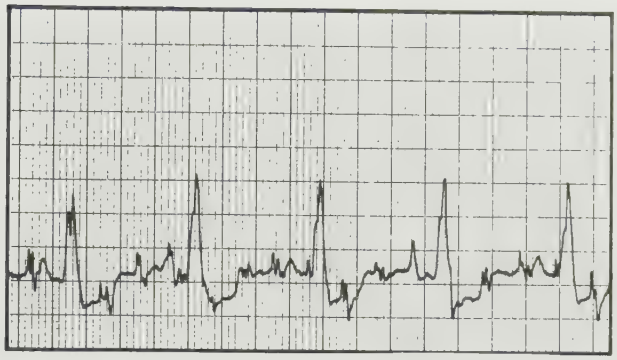


Fig. 45–84. Artifact parasystole. This tracing was recorded on a telemetry unit while a patient was brushing her teeth. The QRS complexes are regular and the artifact is somewhat irregular and occurs at approximately 300 times/min. The artifact, which simulates P waves, has a fairly regular interval between spikes, but is unrelated to the QRS complexes. Also, preceding the first, third, and fifth QRS complexes, the true P waves can be seen in the tracing.

tifacts are "narrower" than a normal QRS and some artifacts last longer than even the most prolonged bundle branch block pattern (Figs. 45–74 and 45–79).

2. If a wave has the appearance of a "QRS complex" but is not followed by a T wave, an artifact should be suspected (Fig. 45–80).
3. Artifacts may be accompanied by a shift in the base line (Fig. 45–81).
4. An artifact that repeats itself must be differentiated from tachycardia. In a repetitive artifact the rate may be too rapid to be physiologically possible. The maximum regular atrial or ventricular rate is approximately 450 beats/min in an infant (130 msec between waves) and 300/min in a child (200 msec between waves). Therefore if there is less than 130 msec between successive regular waves in an infant, or less than 200 msec in a child, an artifact should be suspected (Fig. 45–82).

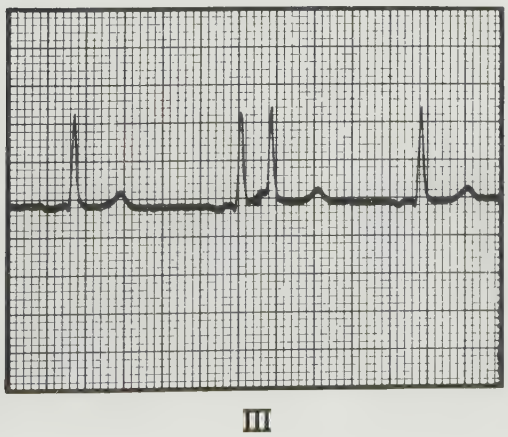


Fig. 45–83. Unphysiologically premature. This tracing was recorded from a normal 14-yr-old. The third QRS complex occurs 180 msec after the last QRS. This is not physiologic. The cause of the artifact can be established by the shift in the base line and the burned appearance to the paper. The electrocardiograph was stopped and started at this time.

A single artifact must be distinguished from a premature beat. Some artifacts occur "too early" to be physiologically possible. The normal atrial or ventricular effective refractory period is approximately 200 msec in an infant and 250 msec in a child. Thus at least this amount of time is necessary before the atrium or ventricle can depolarize again. Therefore if there is, for example, a wave that follows a QRS complex by 180 msec in a 14-year-old, this second wave is unlikely to be a QRS complex (Fig. 45–83).

5. Repetitive artifacts may simulate parasystole. The artifact will usually occur at a variable interval from the preceding P wave or QRS complex, but there may be a constant interval between the artifacts (Fig. 45–84).
6. The basic rhythm is unaffected by the artifact. An artifact may only affect part of the QRS, in which case the QRS may be "seen through" the artifact (Fig. 45–85). Alternatively, the basic R–R interval may be entirely unaffected by the artifact and the QRS "marches through" with the artifact present or absent (Fig. 45–86). In general, following an episode of supraventricular or ventricular tachycardia, the sinus node is suppressed and takes a few beats to regain its normal regular rate. Following a repetitive artifact, the sinus rate does not change, making preceding tachycardia less likely (Fig. 45–87). Finally, if a T wave is the first complex to follow a pause, the pause must have been artifactual since a T wave is unlikely without a preceding QRS complex (Fig. 45–88).
7. Artifacts may be phasic with external influences. Knowledge of the rate of the artifact may help to predict the external

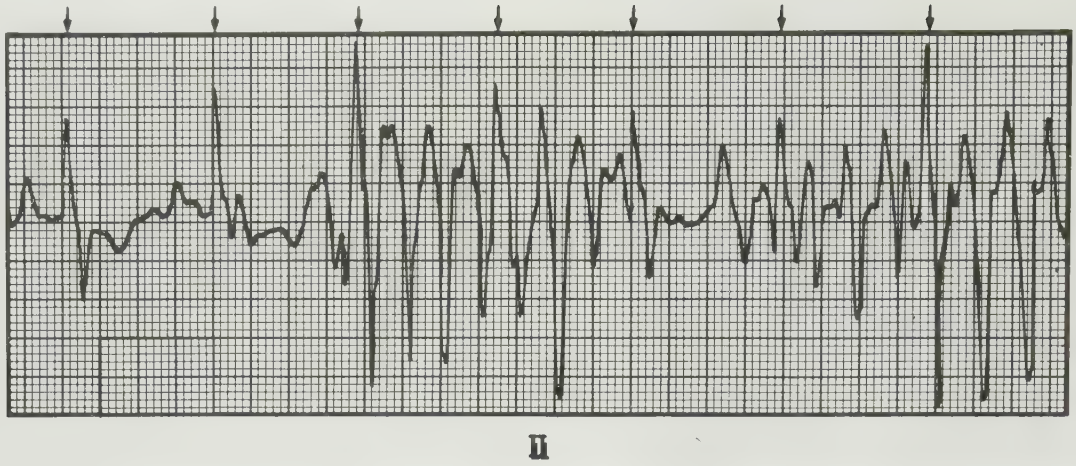


Fig. 45–85. QRS "seen through" the artifact. The arrows mark the QRS complexes, which continue undisturbed through the movement artifact.

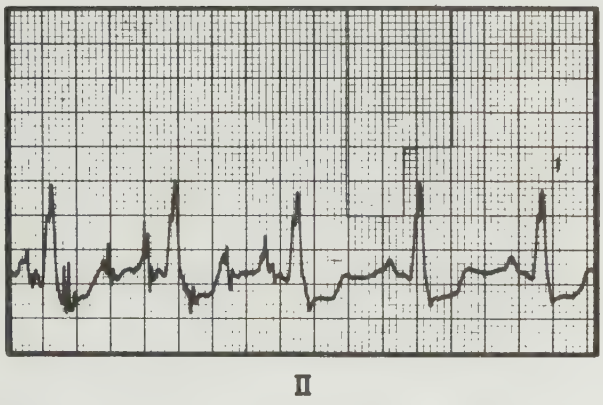


Fig. 45–86. QRS "marches through" the artifact. In the patient who was brushing her teeth during the recording in Figure 45–84, the tooth brushing stopped in this recording and the basic rhythm continued unaffected.

source. The infusion pump artifact shown in Figure 45–78 occurred at the same rate as the infusion: 56 times/min (interval, 1.07 sec between artifacts). Muscle movement related to respiration should occur between 15 and 60 times/min (interval, every 1 to 4 sec) (Fig. 45–70); or tooth brushing occurs at approximately a rate of 300/min (interval of 200 msec) (Fig. 45–84).

8. Artifacts usually occur more than once. Therefore even if a wave on the electrocardiogram cannot be positively identified as either due to depolarization of the heart or due to an artifact, further observation of the remainder of the tracing or a subsequent tracing (perhaps under different circumstances with a more rapid or slower heart rate) will usually reveal the true identity (Fig. 45–89).

Despite all the guidelines, occasionally it is impossible to distinguish artifact from arrhythmia (Fig. 45–90). In these cases clinical correlation is mandatory. A faulty interpretation of an

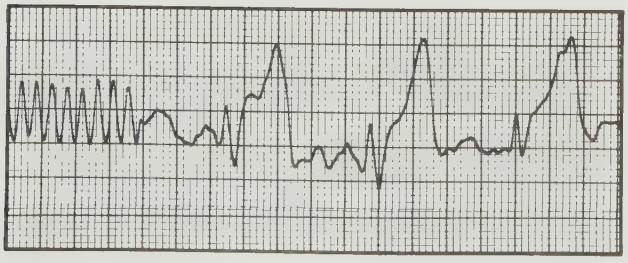


Fig. 45–87. Lack of "sinus pause." The absence of a pause in the rhythm following a rapid rate may be an indication that the rapid rate was an artifact. In this tracing, the rapid artifact stops and there is no pause in the QRS rate.

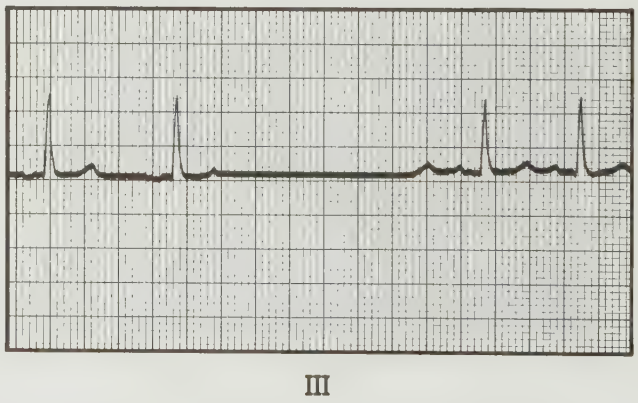


Fig. 45–88. Pause ends with a T wave. The pause in this tracing might have been real except for the undue evenness of the base line and the fact that the pause ends with a T wave, implying that there must have been a QRS complex preceding the T wave, which was not recorded.

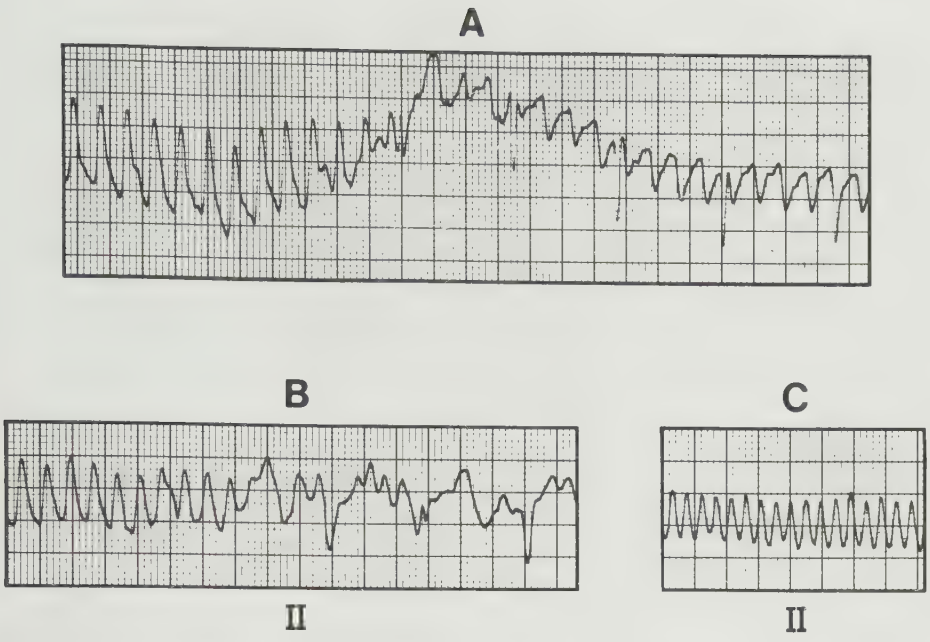


Fig. 45–89. Identification of an artifact at a different point in time. These tracings were both recorded from a 24-hr electrocardiogram. In the first tracing (A), it is not possible to identify the rhythm. It appears that there is a rapid, wide QRS rhythm that inexplicably changes to a rhythm simulating atrial flutter with block. (B) Four hours later, the artifact has a similar morphology but actually disappears before the last QRS complex in the tracing. (C) The artifact has become even smaller in size and now has an unphysiologic rate, identifying the entire process as an artifact.

artifact may cause an "electrocardiographic casualty." Sometimes these casualties are fatal.

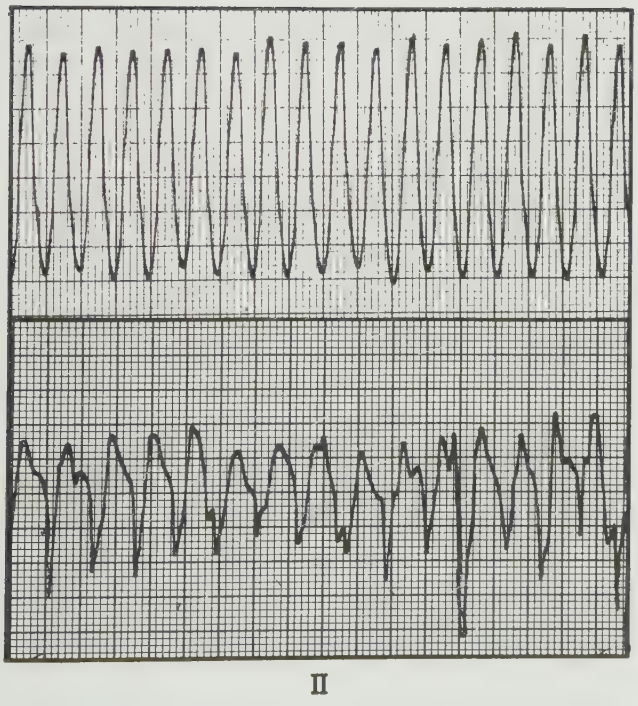


Fig. 45–90. Which is the artifact? The top tracing is ventricular tachycardia; the bottom tracing is the artifact.

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CHAPTER 46

Echocardiography, Two-Dimensional and M-Mode

James C Huhta

The ability to make ultrasonic images of the heart and cardiovascular system (echocardiography) has been a major advance in pediatric cardiology in the past ten years. It has allowed for imaging of anatomy and observations relevant to ventricular function appraisal. This noninvasive modality has dramatically altered the assessment of the neonate with congenital heart disease. It may be said that this technique has slowly changed the practice of pediatric cardiology by replacing cardiac catheterization for the diagnosis of many congenital malformations of the neonate and young child. Combined with the clinical use of prostaglandin for maintenance of patency of the ductus arteriosus, echocardiography has dramatically reduced the need for emergency cardiac catheterization in the neonate.

PHYSICS OF CLINICAL ULTRASOUND

The details of this topic are presented in Chapter 33, only a brief review will be given here. Diagnostic ultrasound for imaging of tissue structures uses the amplitude of backscattered sound from tissue interfaces to construct an image. Sound is transmitted from a transducer in approximately 1000 short burst (pulses) each second. Between transmitted pulses, the returning echoes from the tissue are sensed. Ultrasonic pulses are transmitted through tissue as longitudinal waves and the length of a wave is the distance between two pulses and their respective compression waves in the tissue. The velocity of sound in the tissue is a characteristic of it and is approximately 1540 m/sec. The velocity of sound (c) is the product of the frequency of the sound and the wave length. For example, at 3 megahertz (3 million times per second) the wave length in tissue is 154,000 cm/sec and the wave length is the quotient of the two: 0.051 cm or 0.51 mm. This parameter is an important factor in the theoretical limitation on the resolving power of ultrasound and illustrates that better resolution requires higher insonating frequencies. The returning ultrasound echoes are of a much lower amplitude than those transmitted and are on the order of 0.01% (−40 decibels) of the transmitted intensity. This is because tissue absorption increases with increasing frequency. Therefore, a low frequency transducer will penetrate tissue well but have lower optimal resolution. An ultrasonic display is possible because the time for returning echoes can be converted into distance from the transducer by assuming a constant velocity of ultrasound in tissue.

Principles of Imaging

The concept of resolution may be thought of in three dimensions: axial, lateral, and azimuthal. Axial resolution is the ability of the beam to separate two objects lying along the axis of the beam and is determined primarily by the insonating frequency. Lateral resolution is the ability to separate two objects lying side by side and is determined primarily by the transducer crystal focusing. Azimuthal resolution in the third dimension is also dependent on the beam width. A-mode imaging refers to a series of amplitude spikes representing the returned echo reflections, which are separated by a distance proportional to the time difference in the returning echoes. Turning these spikes on end, so to speak, allows us to see the structure causing the reflections as a dim or bright dot, depending on the amplitude and the motion of the dots with time. An M-mode echo is the time-dependent display of the motion of returning echoes as described above. Alternatively, after individ-

ual lines of ultrasonic data are built up into an image, these can be observed on a cathode ray oscilloscope and the motion of an ultrasound plane is adjusted to allow visualization in real time of moving structures (two-dimensional echocardiography).

DIAGNOSIS OF CONGENITAL HEART DISEASE

Echocardiography has been and will continue to be the mainstay of diagnosis of congenital heart disease in neonates, infants, and children, and it will likely become more important with time as further experience is accumulated. Pioneered by Van Praagh[1] for a description of congenital cardiac defects at the autopsy table, the segmental approach has since been applied to cardiovascular diagnosis by various methods. A logical analysis of cardiovascular anatomy requires a step-by-step segmental approach. This is particularly true in complex congenital malformations where some portions of the heart may be absent or malpositioned. Several recent papers have outlined this concept in the angiographic diagnosis of cardiac anatomy.[2] Data for this interpretation is obtained by combining findings from several echocardiographic windows.[2,3] A complete, step-by-step approach to cardiac diagnosis includes atrial situs diagnosis, identification of chambers and their interconnections, plus a systematic assessment of valves, septa, coronaries, systemic and pulmonary veins, and aortic anatomy.

In review articles, Sanders[4] and Silverman[5] pointed out the need for a complete segmental examination both inside and outside of the heart. The diagnostic accuracy of two-dimensional echocardiographic imaging in children has been proven in several prospective studies including that of Gutgesell et al.[6] In 250 consecutive children with congenital heart disease, there was one surgically significant error in diagnosis.[7] The segmental approach based on the condition that all aspects of abnormal cardiovascular morphology can be broken down into discrete, mutually exclusive descriptors so that any complex congenital malformation can be described unambiguously. Therefore, such a schema must include information on the presence, position, and connection of each cardiac segment.[8] Classically, three segments have been recognized: the atria, the ventricles, and the great arteries. In complex malformations it is necessary to have a detailed approach to segmental diagnosis that can be utilized for noninvasive examination in any setting. By describing sequentially the anatomic segments and indicating normal or abnormal, a complete description of the cardiac anatomy is possible.

Echocardiography is purely a tomographic anatomic tool, but it also provides dynamic information concerning cardiac function and structure. Doppler echocardiography can provide functional information that is not available from any other methodology; for example, atrioventricular valve regurgitation can be diagnosed. However, the grading of regurgitation is currently difficult and depends on many technical and physiologic factors. In addition to seeing a ventricular septal defect, the jet of left-to-right shunt can be detected by pulsed Doppler, the pressure gradient quantitated by continuous-wave Doppler, and spatially oriented by color Doppler. Function description should be integrated into this approach—using the anatomic segment as the finding and the functional aspect as the modifier. For example, left ventricular shortening fraction is appended to the anatomic finding of left ventricular dilation, or "pulmonary valvular stenosis-severe, peak Doppler velocity of 4.2 meters per second." (See Chapter 34.)

Historically, nearly all early two-dimensional echocardiographic literature was oriented toward a "view approach" to congenital cardiac lesions, that is, the appearance of a given cardiac lesion in a standard parasternal, apical, or subcostal scan. This process can lead to diagnostic errors, e.g., a scan of aortopulmonary window from the right ventricular outflow tract can simulate origin of the aorta from the right ventricle (transposition of the great arteries). It is mandatory to integrate various views scanning from one to another from all echocardiographic windows in order to perform a complete anatomic examination. Although the echocardiographic examiner with experience learns the normal appearances of the heart without congenital defects from various echo windows, a structure oriented or anatomic approach is always superior to one based on standardized views.

Situs

Diagnosis of cardiac position and atrial-visceral situs using echocardiographic signs is a standard part of the assessment of congenital heart disease. Atrial situs and atrial morphology are diagnosed together and there are four possibilities: solitus (normal), inversus, and two types of heterotaxy, right atrial isomerism or left atrial isomerism. For example, if the situs is solitus, then the morphologic right atrium is on the right and the morphologic left atrium is on the left. Abnormal atrial situs is frequently associated with cardiac malposition, such as dextrocardia.[9] Both can be diagnosed by obtaining a short axis scan of the abdomen, identifying the spine and the left and right chest cavities. The location of the cardiac apex is important to identify for later scanning from the apex. Subcostal scanning above the diaphragm immediately shows the position of the cardiac apex. From this scan below the diaphragm, the position of the inferior vena cava and aorta can usually be identified. The descending aorta and the inferior vena cava are symmetrically oriented with respect to one another with the inferior vena cava to the right in situs solitus and to the left in situs inversus.[10] In right atrial isomerism the aorta and the inferior cava run together on either side of the spine with the cava anterior (Fig. 46–1). A venous structure that courses behind the aorta and does not enter the heart suggests azygous continuation of the inferior vena cava, which is associated with left atrial isomerism. Such patients nearly always have anomalous hepatic venous connection separately to the heart. Occasionally, atrial appendage morphology can be identified and the diagnosis of atrial situs confirmed directly (Fig. 46–1). A broad-based atrial appendage is usually a morphologic right appendage and a narrow-based appendage is morphologic left. Symmetrical appendages suggest atrial isomerism (Fig. 46–2). A prospective study of the accuracy of indirect methods showed a sensitivity of 100% and a specificity of 99% for detection of abnormal situs by echocardiography using all the above anatomic clues.[11]

Atrioventricular Connection

The diagnosis of connection of the atria and ventricles (atrioventricular connection) requires knowledge of the atrial morphology (see above) and the ventricular morphology (Fig. 46–3). The morphologic left ventricle can be identified by its usual ellipsoidal appearance, two papillary muscles, mitral-semilunar continuity, and the typical mitral valve "fishmouth" appearance.[12] The most reliable criterion for identification of the morphologic right ventricle is tricuspid valve chordal attachments to the septum.[13]

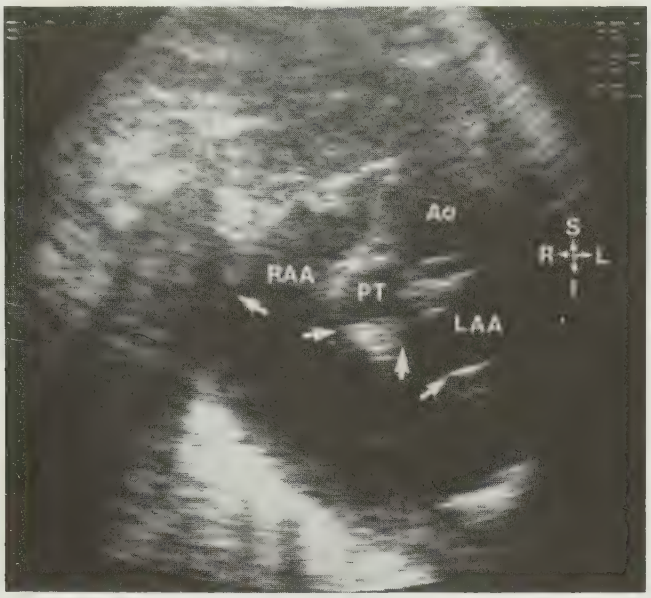


Fig. 46–1. High parasternal imaging of the great arteries (aorta-Ao and pulmonary trunk-PT) showing the normal morphology of the right (RAA) and left (LAA) atrial appendages. I = inferior; L = left; R = right; S = superior; Ao = aorta.

Fig. 46–2. High parasternal imaging of bilateral right atrial appendages (RAA) resembling "dog ears" in a neonate with pulmonary atresia. Ao = aorta. (Reproduced with permission from Huhta, J.C.: Pediatric Imaging/Doppler Ultrasound of the Chest. Philadelphia, Lea & Febiger, 1986, p. 172.)

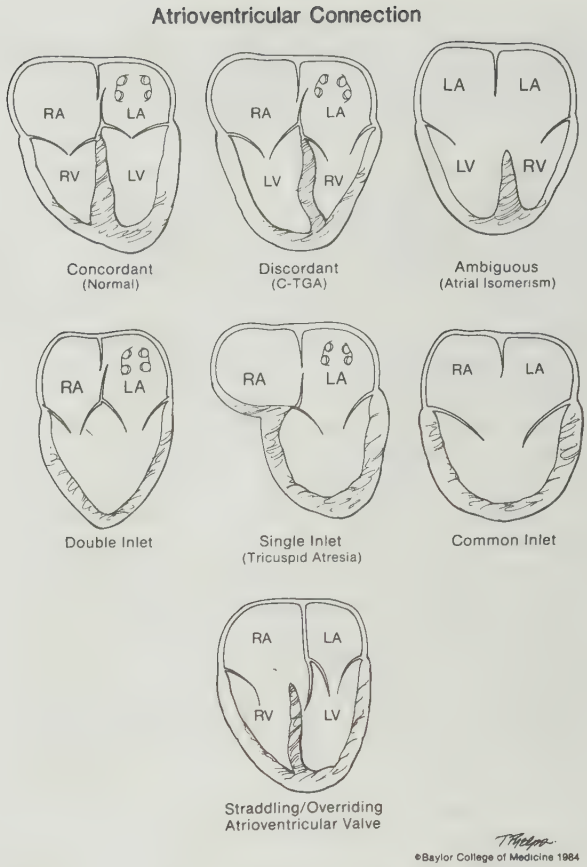


Fig. 46–3. From an apical approach the diagnosis of the atrioventricular connection can be made. *Top row:* In normal (concordant) atrioventricular connection the right atrium (RA) connects normally to the right ventricle (RV). The morphologic left atrium (LA) connects to the morphologic left ventricle (LV). Discordant atrioventricular connection is found in corrected transposition of the great arteries (C-TGA). The right atrium connects to the left ventricle and the left atrium to the right ventricle. In such patients, there is also ventriculoarterial discordance (see below). Ambiguous atrioventricular connection occurs when bilateral left or right atria are present and there are two ventricles. *Middle row:* Univentricular atrioventricular connection is where all the atrial connection is to one ventricle. This abnormal connection may be via two valves (double inlet) (left figure), single inlet with mitral or tricuspid atresia (middle figure), or common inlet where the left and right atria drain to one ventricle via a common AV valve. In rare anomalies with severe straddling or an overriding of an atrioventricular valve, one atrium may drain to more than one ventricle. (Reproduced with permission from Huhta, J.C., et al.: Segmental analysis of congenital heart disease. Dynamic Cardiovasc. Imag. J., *1*:119, 1987.)

There are four possibilities for atrioventricular connection: 1) concordant; 2) discordant; 3) univentricular: single inlet (tricuspid or mitral atresia), double inlet (Fig. 46–4), and common inlet; and 4) ambiguous (in the case of two ventricles with atrial isomerism). When the morphologic right atrium connects normally to the morphologic right ventricle and the left atrium connects to the left ventricle, there is atrioventricular concordance (normal). When this connection is reversed and the morphologic right atrium connects to the morphologic left ventricle, there is atrioventricular discordance, sometimes referred to as ventricular inversion.[13] Pa-

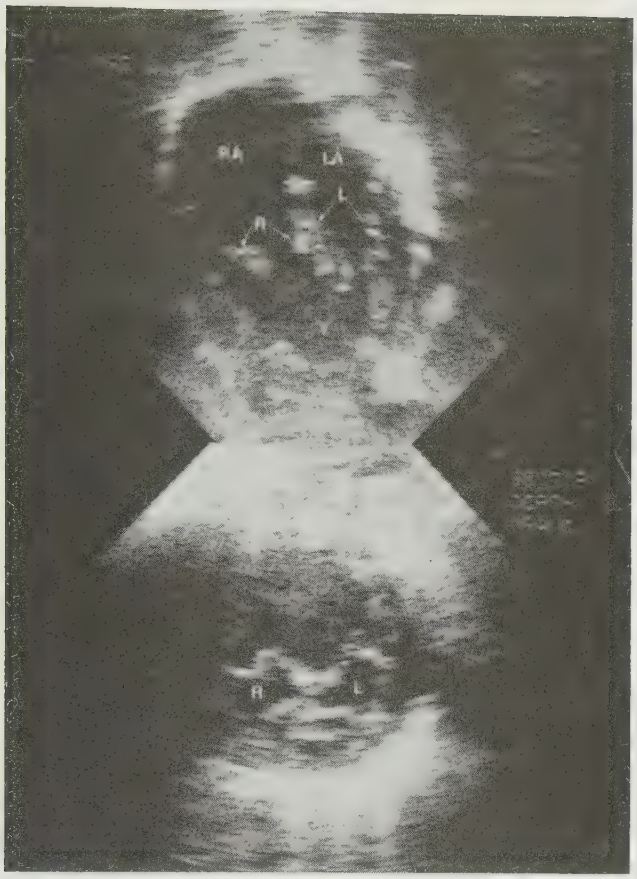


Fig. 46–4. Double inlet ventricle (V) from an apical (upper panel) and short axis scan (lower panel). Both the left (LA) and the right (RA) connect to the same ventricle.

tients with such abnormalities may present with complete AV block and have a high incidence of associated congenital cardiac malformations such as ventricular septal defect and pulmonary stenosis and usually also have ventriculoarterial discordance (see below). Rarely, atrioventricular discordance may occur while the ventriculoarterial connection is normal. When the majority of atrioventricular connection is to one ventricle, the connection is univentricular via either one valve (single inlet with atresia of the other valve), double inlet (two atrioventricular valves), or common inlet (via a common atrioventricular valve). Common inlet ventricle is part of one end of the spectrum of atrioventricular septal defect (AV canal) where there is hypoplasia of one of the ventricular chambers and atrioventricular connection is predominantly to the other.[14]

The accuracy of echocardiographic imaging in the diagnosis of atrioventricular connection is unsurpassed by other modalities.[15,16] Occasionally, an inexperienced observer may observe a common inlet that has a common (four leaflet) valve and confuse it with a single inlet. After experience with imaging the variations of atrioventricular septal defect this should not present problems.[17] Identification of the lower atrial septum unequivocally identifies the crux of the heart and points to a single inlet with atresia of the other valve.

Ventriculoarterial Connection

Ventriculoarterial connection is the manner in which the great arteries and semilunar valves connect to the ventricular outflow tracts (Fig. 46–5). There are four possibilities: concordant (normal), discordant (right ventricle to aorta and left ventricle to pulmonary trunk), double outlet (usually right ventricle), or single outlet (with aortic or pulmonary atresia or truncus arteriosus). Normally the morphologic right ventricle connects to the pulmonary valve and the morphologic left ventricle connects to the aortic valve.

Ventricular Morphology

Determination of the atrioventricular and ventriculoarterial connections requires a knowledge of ventricular morphology and this

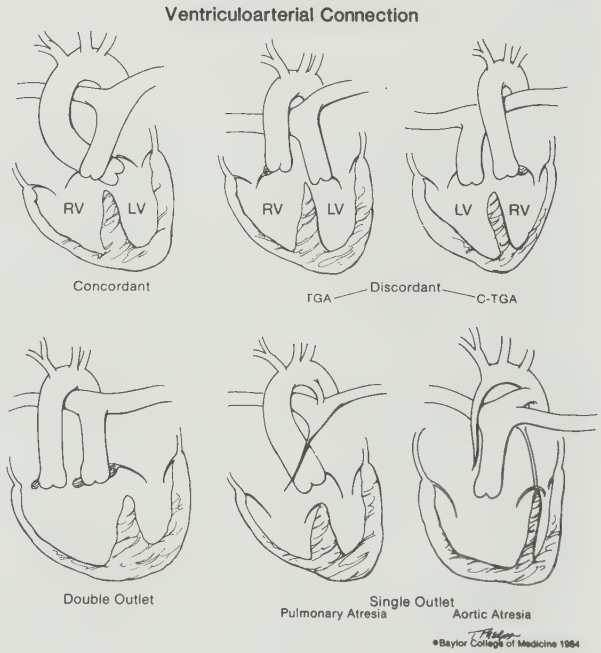


Fig. 46–5. Diagnosis of ventriculoarterial connection. Normal (concordant) ventriculoarterial connection connects the left ventricle to the aorta and the right ventricle (RV) to the pulmonary artery. Discordant ventriculoarterial connection may occur with transposition such that the right ventricle connects to the aorta and the left ventricle to the pulmonary artery. Both great arteries may arise from either ventricle but most commonly, a double outlet ventricle is a double outlet right ventricle (left lower figure). Single outlet hearts include those with truncus arteriosus but also those with pulmonary or aortic atresia (middle and right lower figures). (Reproduced with permission from Huhta, J.C., et al.: Segmental analysis of congenital heart disease. Dynamic Cardiovasc. Imag J., *1*:120, 1987.)

should be one of the first steps in noninvasive diagnosis. Criteria for a morphologic left ventricle by echocardiography includes insertion of the mitral valve at the base of the heart farther from the cardiac apex than the tricuspid valve (so-called "offsetting" of the valves), two normally placed left ventricular papillary muscles, mitral semilunar continuity, typical elliptical shape, smooth wall septum, and fishmouth appearance of the mitral valve with two commissures. In the absence of typical offsetting of the atrioventricular valves and with cardiac malposition, the trabecular pattern of the ventricles can sometimes be recognized, i.e., smooth-walled in the left ventricle and coarser, more heavily trabeculated, in the right ventricle. The appearance of the ventricular outflow tracts may aid in ventricular morphology diagnosis and should be noted as part of the segmental approach. There is normally continuity between the mitral valve of the left ventricle and the aortic valve, whereas there is muscle separating the tricuspid and the pulmonary valve in the right ventricular outflow tract.

The most common type of abnormality of ventriculoarterial connection is transposition of the great arteries (TGA) where the morphologic right ventricle gives rise to the aorta and the morphologic left ventricle gives rise to the pulmonary trunk (ventriculoarterial discordance) (Fig. 46–6). In order to diagnose this abnormality, it is necessary to identify the great vessels. The pulmonary artery is identified by its branching pattern into left and right pulmonary arteries and ductus arteriosus, and the aorta is identified by the carotid and subclavian arteries. Both great vessels may originate from either ventricle (usually the morphologic right ventricle) creating double-outlet right ventricle. If the aortic or pulmonary valve is atretic, then a single-outlet ventricle is the result. Another example of single outlet is truncus arteriosus where there is a single trucal valve originating from the ventricular mass but overriding of the ventricular septum. The ventriculoarterial connection is designated single outlet with overriding truncal valve. In complex malformations including right atrial isomerism with the asplenia syndrome, atrioventricular septal defect is often associated with double-outlet right ventricle (Fig. 46–7). With tetralogy of Fallot there is often overriding of the aortic valve so

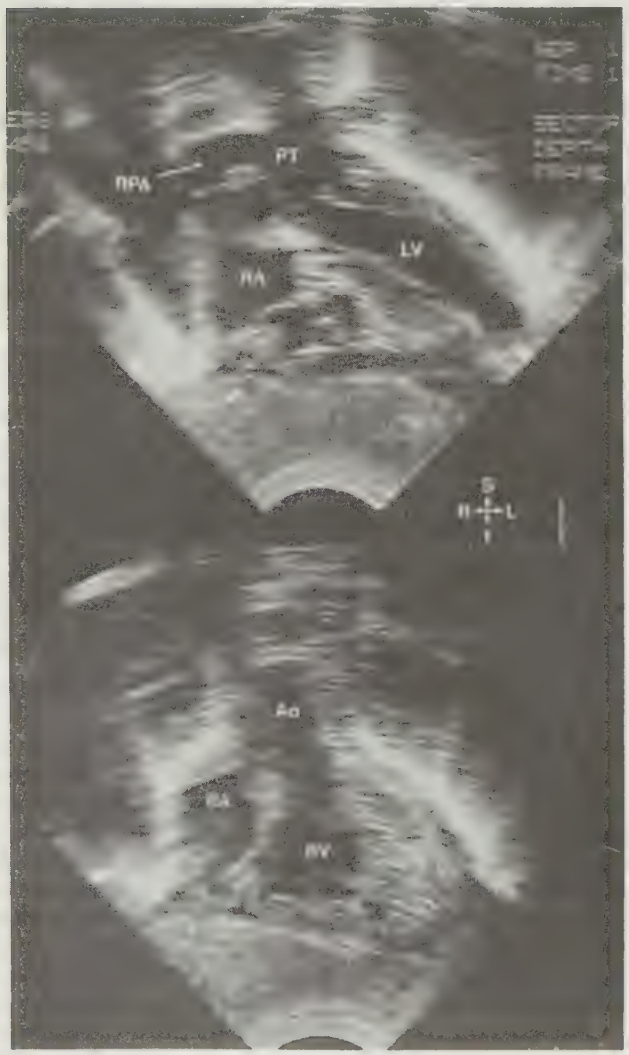


Fig. 46–6. Subcostal imaging of a neonate with transposition of the great arteries. The left ventricle (LV) connects to the pulmonary trunk (PT) (upper panel) and the right ventricle connects to the aorta (Ao). RA = right atrium.

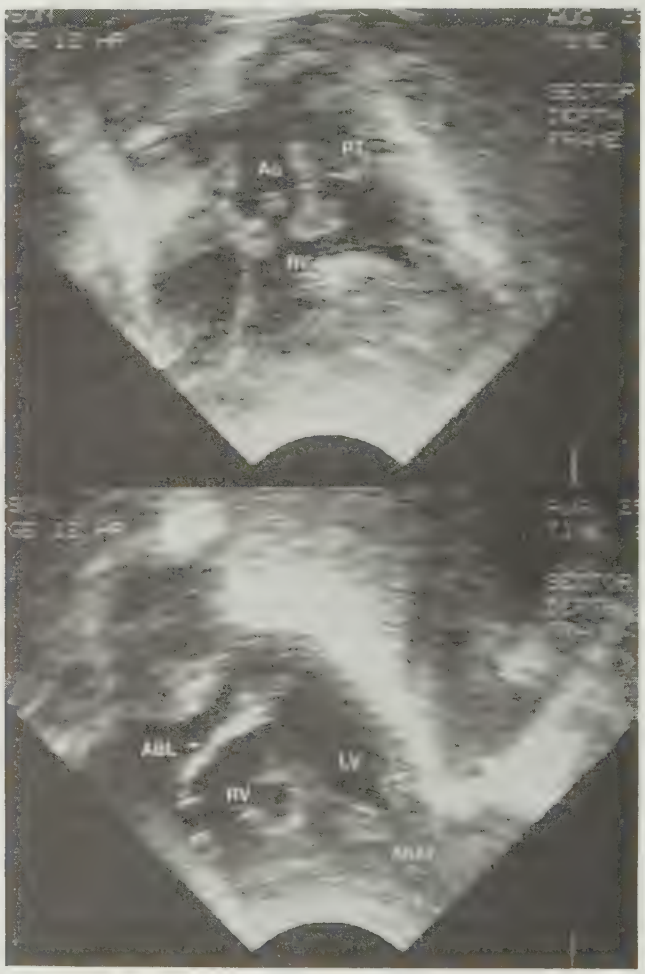


Fig. 46–7. Subcostal scanning of a neonate with double outlet right ventricle with the aorta (Ao) to the right of the pulmonary trunk (PT). The ventricular anatomy is complete atrioventricular septal defect with a freefloating anterior bridging leaflet (ABL). LV = left ventricle.

that nearly half of the aortic valve anulus appears to arise from the right ventricle. There is mitral aortic continuity and, except for the rare circumstance where there is more than 50% overriding of the aortic valve, the ventriculoarterial connection in tetralogy of Fallot is concordant.

Reports in neonates with abnormalities of ventriculoarterial connection and in children with transposition of the great arteries show that echocardiography is highly accurate in this type of abnormality.[18,19,20] Consequently, a newborn with cyanosis due to transposition should virtually never be discovered during the catheterization and some such neonates have had surgery without catheterization.

Ventricular and Atrial Septae

Atrial Septum

Prior to birth the atrial septum usually bows toward the morphologic left atrium due to the significant blood flow to the left heart via the fossa ovalis (Fig. 46–8). Such aneurysmal bowing of the atrial septum after birth may be a clue to right-to-left intra-atrial shunting (or left-to-right if it is bowing toward the right atrium). Results by imaging alone in detection of atrial septal defect are good.[20] The presence of a thin strand of septal tissue in what appears to be a common atrium is highly suggestive of right atrial isomerism. The upper atrial septum where a sinus venosus defect may occur can be difficult to evaluate in the older child but color flow mapping has improved the results in all forms of atrial septal defect.[21] In the prospective study of Gutgesell there was one false positive and one false negative for sinus venosus defect.[6] One practical application of echocardiography is evaluation of the results of creation of an atrial defect by balloon atrial septostomy or blade and balloon techniques (Fig. 46–9).

Ventricular Septum

Defects of the ventricular septum can be analyzed using multiple tomographic imaging approaches and defects can be separated into those which are perimembranous, muscular, and subarterial (see Fig. 46–4).[22] An inlet perimembranous defect (AV canal-type defect) can be distinguished from AV canal by the presence of the central fibrous crux (Fig. 46–10). Small muscular ventricular septal defects and even a significant defect in the perimembranous region may be missed by imaging alone (Fig. 46–11); color Doppler has substantially improved the ability to detect muscular defects, but the sensitivity in detection of a muscular defect in older children with another large VSD was only 72% in one study.[23] The details of interventricular communications in the trabecular septum require angiographic definition. At present, echocardiography with color Doppler appears adequate only to detect the defect rather than provide details.

Valves

Atrioventricular Valves

A wide variety of malformations may involve the left or right atrioventricular valves. From an anatomic perspective, either the

Fig. 46–8. Five different types of atrial septal morphology. Intact and secundum defect (top) and common atrium (CA), primum defect and atrial strand (S) (lower). LA = left atrium; RA = right atrium. (Reproduced with permission from Huhta, J.C., et al.: Two dimensional echocardiographic diagnosis of situs. Br. Heart J., *48*:106, 1982.)

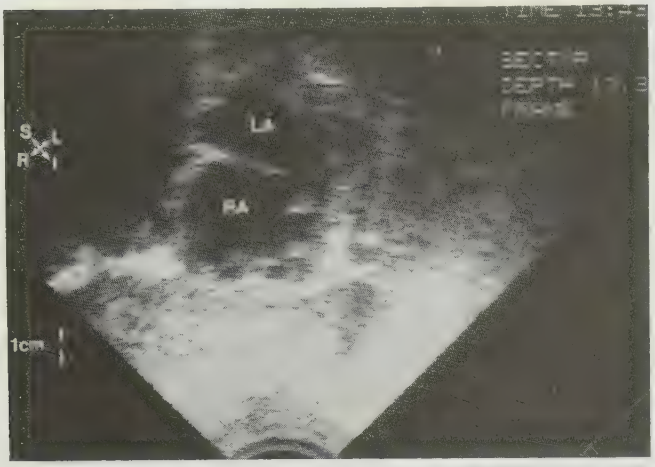


Fig. 46–9. Subcostal imaging of an atrial septal defect created by blade and balloon atrial septostomy. Abbreviations as before.

mitral or tricuspid valve may be abnormal in position, stenotic, regurgitant, have a cleft, be hypoplastic, exhibit prolapse, straddling, or Ebstein's malformation. The pattern of opening on real-time imaging is augmented by the Doppler or M-mode functional assessment. Virtually all forms of congenital anatomic abnormality of the mitral valve can be recognized immediately by imaging alone with the possible exception of supravalvar mitral ring where the ring may be adherent to the valve tissue. The presence of normal papillary muscles in supravalvar mitral ring differentiates it from most other congenital forms of mitral stenosis. Color flow mapping and continuous-wave Doppler can effectively evaluate the hemodynamics of AV valve stenosis better than invasive techniques. Regurgitation of AV valves can be detected with excellent sensitivity and progress is being made with color Doppler at grading the severity of regurgitation of AV and semilunar valves.[24]

Semilunar Valves

Semilunar valve assessment is aimed at detecting obstruction or regurgitation at either the aortic or pulmonary valve. Because the size of a valve anulus will normally reflect the flow through it, hypoplasia of the valve anulus usually is present with severe stenosis and imaging echocardiography may detect this or the doming of a stenotic valve or muscular hypertrophy of infundibular

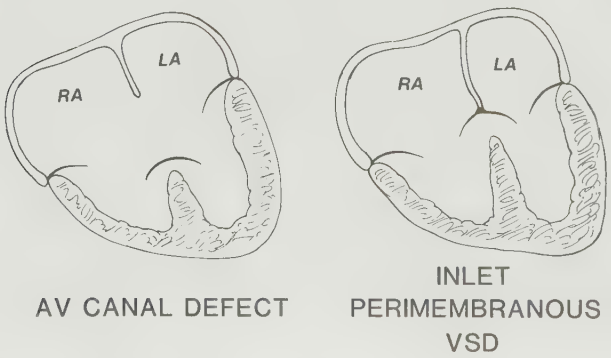


Fig. 46–10. Comparison of atrioventricular (AV) canal defect and inlet perimembranous ventricular septal defect (VSD). In the latter defect the fibrous crux is present.

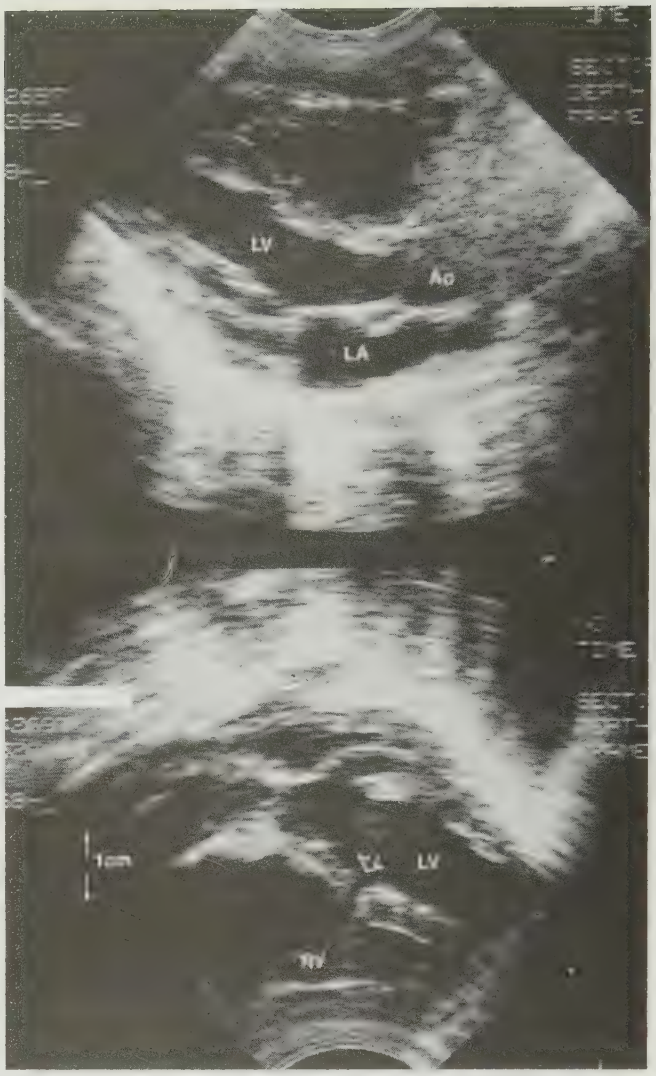


Fig. 46–11. Parasternal (upper) and subcostal (lower) imaging of a small muscular septal defect above the insertion of the moderator band. Ao = aorta; LA = left atrium; LV = left ventricle.

stenosis. Likewise, the abnormal coaptation of semilunar valve cusps indicate regurgitation (Fig. 46–12). In congenital heart disease there was a 77% sensitivity of pulmonary stenosis detection with a specificity of 97%.[6] Both of these numbers are now approaching 100% by application of pulsed and continuous wave techniques.[25] Because of the variability of cardiac output through a stenotic valve, the flow-independent method of the continuity equation looking at the mean velocity may be more useful.

Systemic Veins

Systemic Venous Connections

Normal inferior and superior vena cavae connecting to the right atrium are highly indicative of normal systemic venous connection to the morphologic right atrium. It is important to identify the inferior vena cava connecting to the heart and extending into the abdomen so that hepatic veins connecting separately are not mis-

Fig. 46–12. Abnormal aortic valve coaptation (open arrow in the lower panel) with aortic regurgitation secondary to subacute bacterial endocarditis. AAo = ascending aorta; LV = left ventricle.

taken for it. Systemic venous return which is abnormal in situs solitus may be normal or "usual" in cases where the situs is not solitus. Systemic venous return may be typical of the atrial situs (for example, azygous continuation with left atrial isomerism). Each of the systemic venous segments, including the right superior vena cava, the left superior vena cava, the inferior vena cava, coronary sinus, and hepatic veins should be examined individually. A prospective assessment of this approach showed a sensitivity of over 95% for each segment with the exception of the smaller bridging innominate veins.[26]

Systemic Venous Anomalies

A persistent left superior vena cava (Fig. 46–13) can be detected by echocardiography and confirmed by contrast studies; however, if it appears that the superior vena cava may connect to the left atrium or drain to this site due to unroofing of the coronary sinus, then angiographic confirmation is useful (see Chapter 84 on Systemic Veins).

Pulmonary Veins

Each pulmonary vein must be imaged in a sequential fashion. A four-chamber view will often reveal at least two pulmonary

Fig. 46–13. Persistent left superior vena cava (LSVC) passing anterior to the left pulmonary artery (PA) in a child with corrected transposition.

veins connecting to the left-sided morphologic left atrium, and the right veins can be seen individually from suprasternal scans. Total anomalous pulmonary venous connection can be detected with 85 to 97% sensitivity depending on the experience of the examiner.[6,27] Although accurate diagnosis of isolated total anomalous pulmonary venous connection can be made in neonates and infants, the ability of any noninvasive tool to exclude isolated partial anomalous connection of one vein has not been tested. Color Doppler adds a significant increment in confirming the presence of pulmonary venous flow in the location where the vein is thought to be connecting and the detection of pulmonary venous obstruction is dependent on Doppler.[28]

Direct visualization of all four pulmonary veins is mandatory prior to corrective surgery for any defect but especially those associated with anomalous pulmonary venous connection such as atrial septal defect. Any deviation from usual should prompt complete angiographic study. Patients with atrial isomerism usually have abnormalities of pulmonary venous connection and often require angiography prior to palliative surgery.

Coronary Arteries

A segmental approach is necessary for evaluation of the coronary arteries.[29] With the exception of aneurysm detection in the proximal coronary arteries in Kawasaki disease, the detection of the origin of the common left or right coronary artery, ultrasonography is limited in the definition of abnormalities of the coronary circulation. In the presence of a coronary artery fistula, the enlargement of one of the coronaries can usually be detected. In our experience, an isolated coronary fistula can be repaired without bypass and the entry site can be defined with color Doppler.

Anomalous origin of one or both coronaries from the pulmonary trunk can be detected with high specificity, especially in combination with Doppler,[30] but the sensitivity is not adequate in neonates. The use of 7.5 and 10 MHz transducers can improve these results. Any electrocardiographic evidence of coronary insuffi-

ciency should prompt immediate coronary angiography if surgical intervention is contemplated in anomalous coronary artery.

All patients with tetralogy of Fallot should have definition of the coronaries to define the origin of the left anterior descending branch prior to a right ventriculotomy. Future work in imaging the coronary artery anatomy in tetralogy of Fallot and transposition may help to define the coronaries without need for angiography.

Aorta

Segmental analysis of the aorta includes assessment of the ascending aorta, aortic arch branching, the aortic isthmus, and the descending aorta. Echocardiography is highly accurate in the diagnosis of abnormalities of the aorta in neonates, infants, and children (sensitivity 95%, specificity 99%). Each segment of the aorta is in a slightly different tomographic plane requiring a sequential, segmental approach.[31] Normal branching of the right innominate artery indicates a left aortic arch with normal branching (Fig. 46–14). Such branching of an innominate artery to the left indicates a right aortic arch with mirror image branching (Fig. 46–15). A patent ductus arteriosus is the most common abnormality detected in examination of the aorta and the morphology of the ductus may be helpful. For example, in pulmonary atresia, the ductus is horizontal, unlike normal (Fig. 46–16). The sensitivity of two-dimensional imaging alone in detection of ductus is only 83%.[6]

Coarctation of the aorta, which has a typical appearance in the

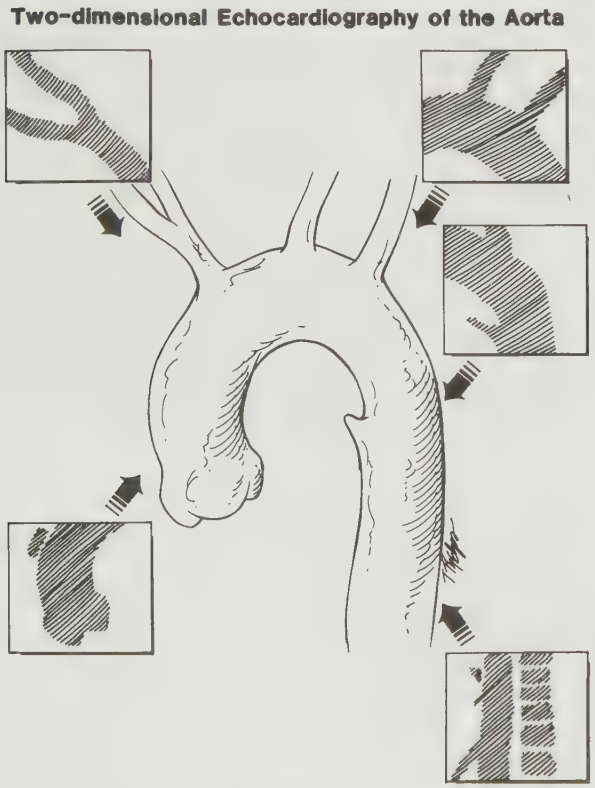


Fig. 46–14. Illustration of segmental imaging of the aorta. (Reproduced with permission from Huhta, J.C., et al.: Two dimensional echocardiographic assessment of the aorta in infants and children with congenital heart disease. Circulation, *70*:418, 1984.)

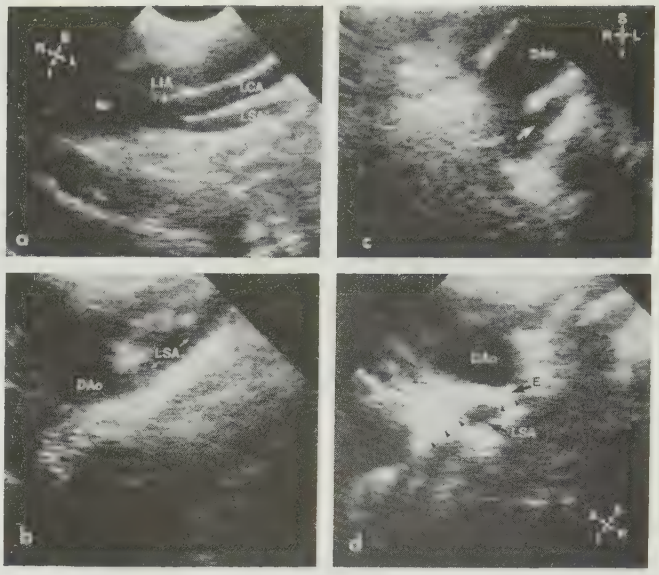


Fig. 46–15. Segmental imaging of right aortic arch with mirror image branching (a) and with anomalous origin of the left subclavian artery (LSA) from the descending aorta (DAo) (b,c,d). Imaging of the esophagus during swallowing confirms the retroesophageal location of the LSA. (Reproduced with permission from Huhta, J.C., et al.: Two dimensional echocardiographic assessment of the aorta in infants and children with congenital heart disease. Circulation, *70*:420, 1984.)

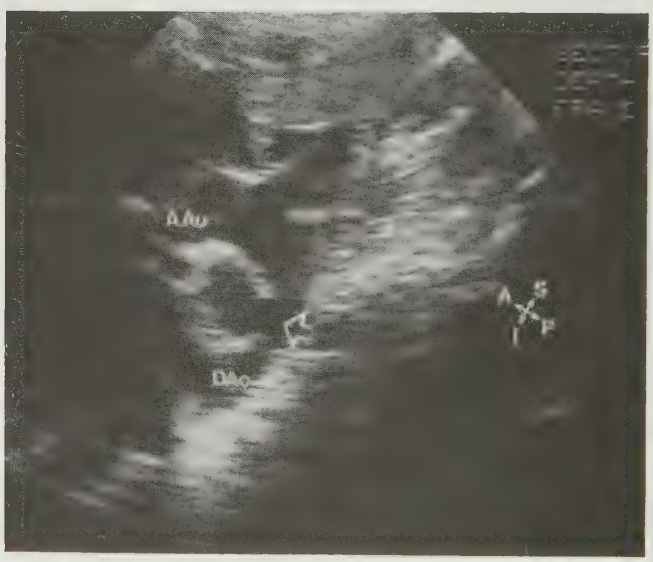


Fig. 46–16. High parasternal imaging of a patent ductus arteriosus in a neonate with pulmonary atresia and intact ventricular septum. The origin is horizontal (open white arrow) which is typical of this lesion. (Reproduced with permission from Huhta, J.C.: Pediatric Imaging/Doppler Ultrasound of the Chest. Philadelphia, Lea & Febiger, 1986, p. 115.)

neonatal period including hypoplasia of the transverse aortic arch, may be diagnosed by echocardiography.[32] This appearance plus the presence of right ventricular enlargement make the diagnosis of coarctation of the aorta possible. The typical Doppler pattern will confirm the diagnosis. In patients with a large ventricular septal defect, the status of the aorta should always be investigated to exclude coarctation. In adults, the segmental analysis of the aorta is less reliable[33] so that Doppler techniques have significantly improved the detection of coarctation in cases where imaging is poor.

Systemic Arteriovenous Fistulae

Systemic arteriovenous fistulae cause enlargement of the artery feeding the fistula and generalized enlargement of the aorta. Pulmonary sequestration and hepatic and cerebral fistulae are the most common systemic fistulae. Sequestration of the lung and other fistulae causing an obligatory shunt can be detected by careful technique and may simulate coarctation of aorta due to the aortic isthmus morphology. Angiography is required for definition of the small vessel anatomy of the fistula before surgery.

Pulmonary Arteries

The most common abnormality of the pulmonary arteries that is indicative of congenital heart disease is pulmonary artery hypoplasia (Fig. 46–17). The pulmonary arteries normally are confluent in the midline and this detail of anatomy has importance in planning a palliative approach to cyanotic congenital heart disease.[34,35] Abnormalities of origin of the pulmonary arteries as well as their size may occur. In severe right ventricular outflow tract obstruction in neonates, pulmonary artery hypoplasia is associated with a reciprocal increase in the size of the aorta so that the ratio of size of the pulmonary arteries to the aorta may be useful in the diagnosis of this abnormality (Fig. 46–18). Diagnosis of the details of the distal pulmonary arteries requires angiography. Magnetic resonance imaging may be helpful in this area. A pulmonary arteriovenous fistula presents with cyanosis and enlargement of the pulmonary arteries and veins on echocardiography and should be confirmed by angiography.

Pulmonary atresia-VSD with major aortopulmonary artery collaterals may be difficult to evaluate. The neonate with pulmonary atresia and ventricular septal defect with collaterals can be differentiated from one with ductus-dependent pulmonary supply by imaging the ductus and well-developed confluent pulmonary arteries. All patients with collateral arteries and multifocal pulmonary supply must have complete angiography prior to any operation.

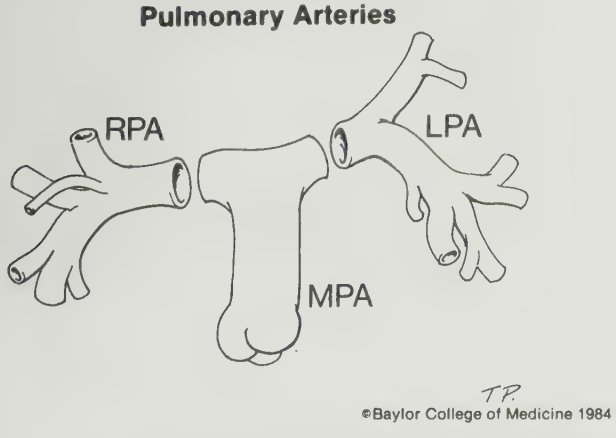


Fig. 46–17. Schematic of the segmental approach to the pulmonary arteries. The main, left and right pulmonaries can be imaged in turn from parasternal and suprasternal scans.

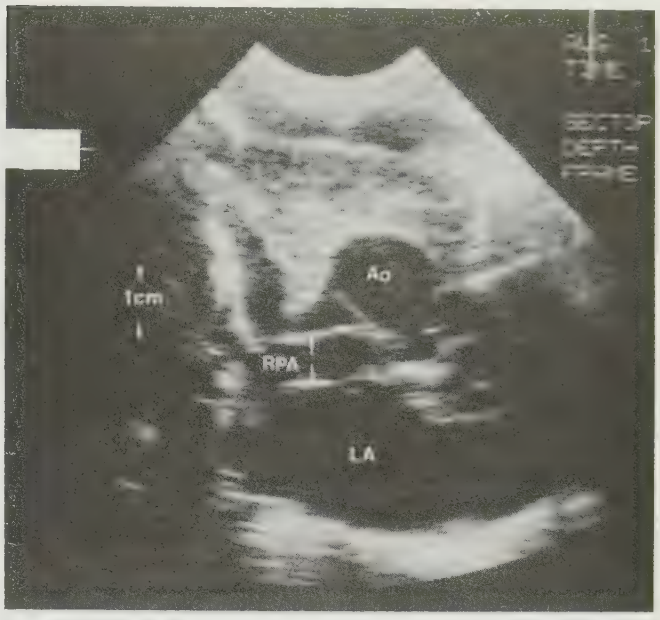


Fig. 46–18. Suprasternal imaging of the right pulmonary artery (RPA) in a neonate with pulmonary stenosis. The artery passes above the left atrium (LA) and posterior to the superior vena cava.

Example of a Clinical Examination

A 26-month-old child was noted to have a heart murmur and the electrocardiogram was "unusual." An echocardiogram was ordered to exclude congenital heart disease. The imaging examination was performed in segmental fashion beginning with the atrial situs determination (Fig. 46–19). The aorta was on the left in the abdomen and the inferior vena cava was on the right connecting normally. The right atrial appendage appeared to be broad-based and normal, suggesting situs solitus, and the position of the aorta and pulmonary trunk were reversed (Fig. 46–20). The atrioventricular connection was abnormal with the left atrium connecting to the left-sided morphologic right ventricle (Fig. 46–21). The right atrium connected to the morphologic left ventricle, which then connected to the pulmonary artery (Fig. 46–22). The aortic valve arose from the morphologic right ventricle (Fig. 46–23) so the atrioventricular and ventriculoarterial connections were discordant ("corrected" transposition). The ventricular septum appeared intact but there was dropout in the fossa ovalis region of the atrial septum (Fig. 46–24), implying an atrial septal defect. Pulmonary veins connected to the left atrium, and the superior vena cava connected to the right atrium. Imaging of the great arteries showed a normal left aortic arch and pulmonary arteries (Fig. 46–25). Doppler evaluation of the left atrioventricular valve (tricuspid valve) showed that the murmur was caused by tricuspid regurgitation (Fig. 46–26). The final diagnosis was "corrected" transposition with systemic atrioventricular valve regurgitation.

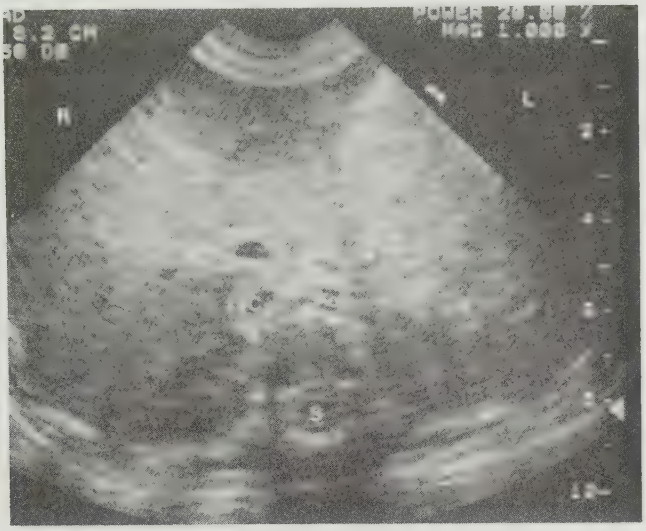


Fig. 46–19. Echocardiographic determination of atrial situs. A subcostal transverse scan of the abdomen immediately below the diaphragm shows the inferior vena cava (IVC) on the right and the descending aorta (Ao) on the left symmetrically related with respect to the spine (S). The liver is normally predominately right-sided at this level of the abdomen.

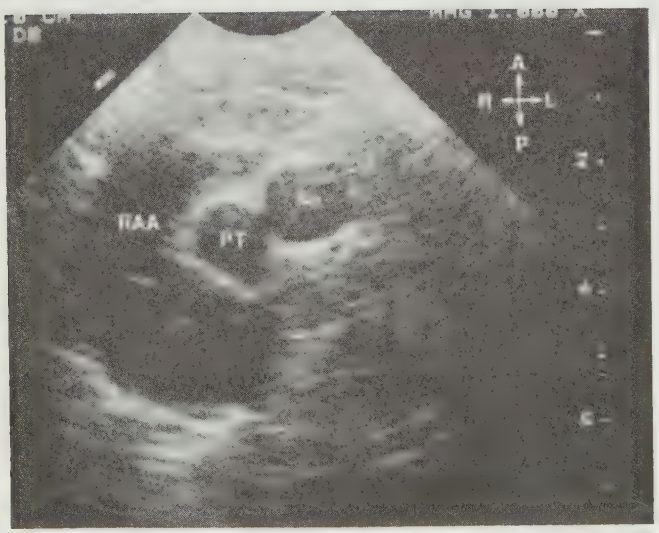


Fig. 46–20. High parasternal transverse scan of the broad-based right atrial appendage (RAA) on the right confirming the normal atrial situs. Note that the aorta (Ao) is anterior and to the left of the pulmonary trunk (PT).

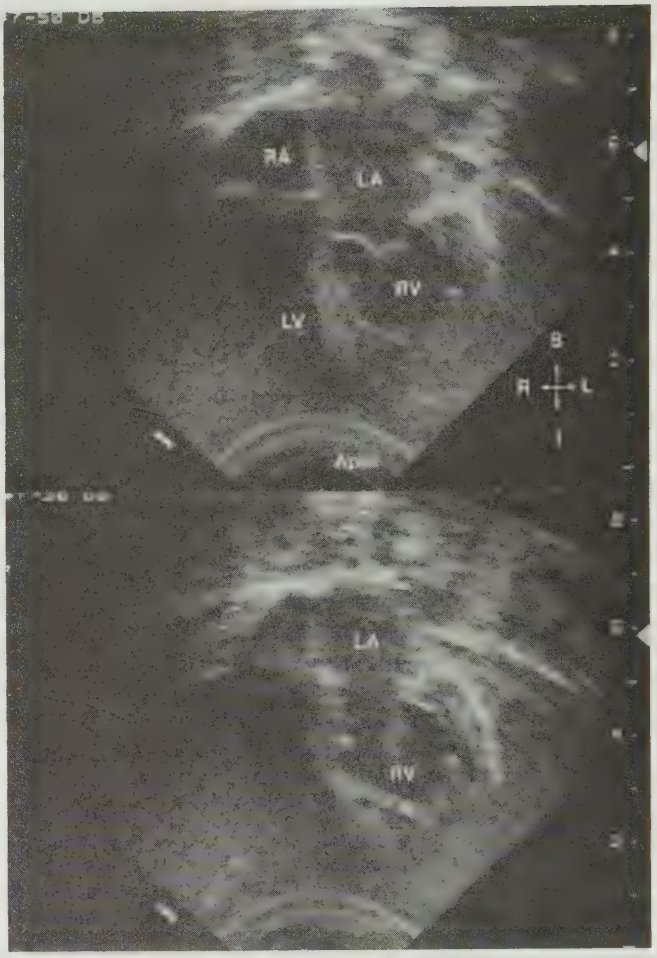


Fig. 46–21. Atrioventricular connection is determined from the apical four-chamber view. The atria are normally related with the morphologic right atrium (RA) on the right and the morphologic left atrium (LA) on the left (further identified by the connection of pulmonary veins). The atrioventricular connection is abnormal (discordant): the right atrium connects to the right-sided left ventricle and the left atrium connects to the left-sided right ventricle. The atrioventricular valve always goes with its ventricle and, in this systolic frame (upper panel), the left-sided tricuspid valve is identified further by its inferior displacement with respect to the right atrioventricular valve. The opening pattern of the left atrioventricular valve in diastole (lower panel) is toward the apex of the ventricle with septal chordal insertions, typical of a morphologic tricuspid valve.

Fig. 46–22. Determination of the ventriculoarterial connection is shown in two subcostal scans. Top: The morphologic left ventricle (LV) receives blood through the mitral valve from the right atrium (RA). The abnormal ventriculoarterial connection (discordant) is recognized by the connection of the left ventricle to the pulmonary artery (PA) which is identified by its continuation to the right pulmonary artery. The continuity of the right atrioventricular (mitral) valve and the pulmonary valve and the smooth-walled appearance of the right side of the ventricular septum confirm this as the left ventricle. Bottom: The connection of the right ventricle (RV) to the left-sided aortic valve (AV) can be seen by scanning more anteriorly.

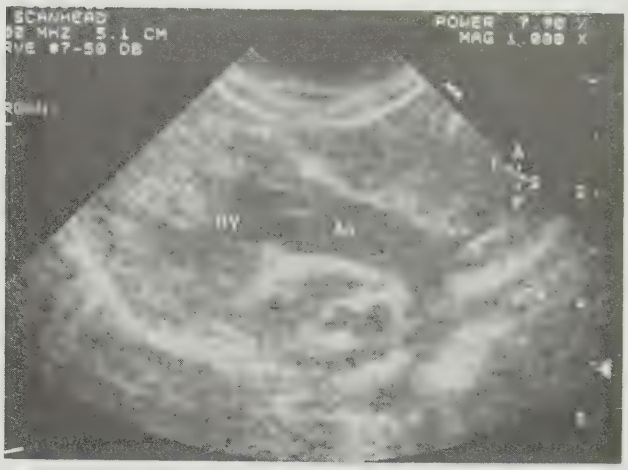


Fig. 46–23. The connection of the morphologic right ventricle (RV) to the aorta (Ao) is confirmed in a high left parasternal scan. There is infundibular muscle under the aortic valve and no continuity with an atrioventricular valve, typical of a right ventricle. The aorta is identified by the origin of the brachiocephalic arteries including the left carotid artery (LCA) from it.

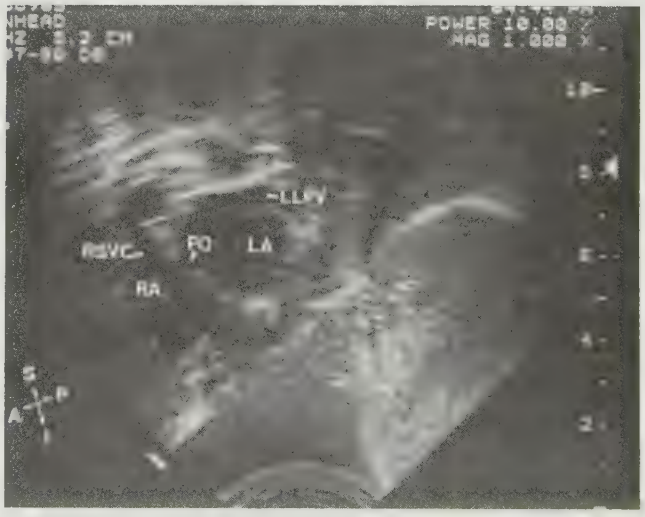


Fig. 46–24. Subcostal examination of the atrial septum. The left (LA) atrium receives connection of the left lower pulmonary vein (LLPV) in this scan and the right superior vena cava (RSVC) is seen entering the right atrium (RA) atria. Dropout in the region of the fossa ovalis (FO) is a normal finding.

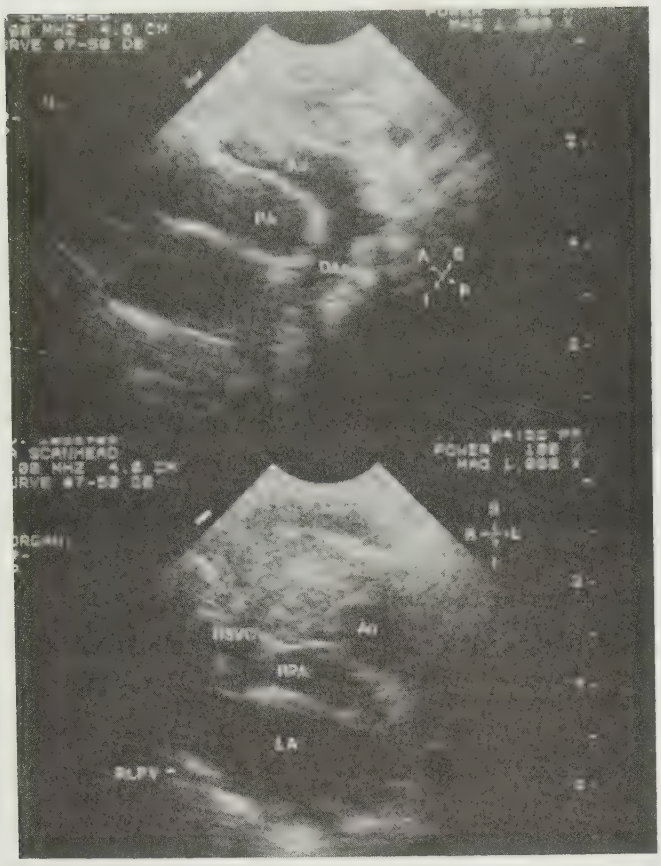


Fig. 46–25. (Upper panel) High parasternal scanning of the aortic arch (Ao) and pulmonary artery (PA). The origin of the left subclavian artery (LSA) is well visualized. (Lower panel) Suprasternal scanning of the aorta (Ao), the right pulmonary artery (RPA), and the left atrium (LA). The connection of the right lower pulmonary vein (RLPV) to the left atrium (LA). The right superior vena cava (RSVC) passes in front of the pulmonary artery.

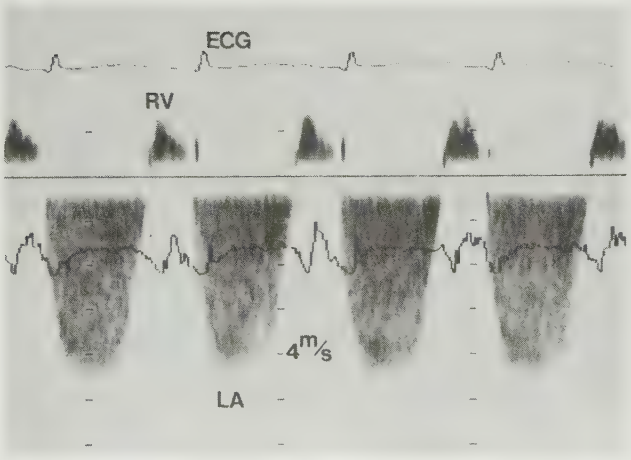


Fig. 46–26. Continuous-wave Doppler of left atrioventricular valve (tricuspid) regurgitation from the right ventricle (RV) to the left atrium (LA) in corrected transposition. The peak velocity is 4.5 meters per second (m/s).

Such a step-by-step evaluation led to the diagnosis by excluding abnormalities of each segment and synthesizing the individual findings.

VENTRICULAR FUNCTION ASSESSMENT

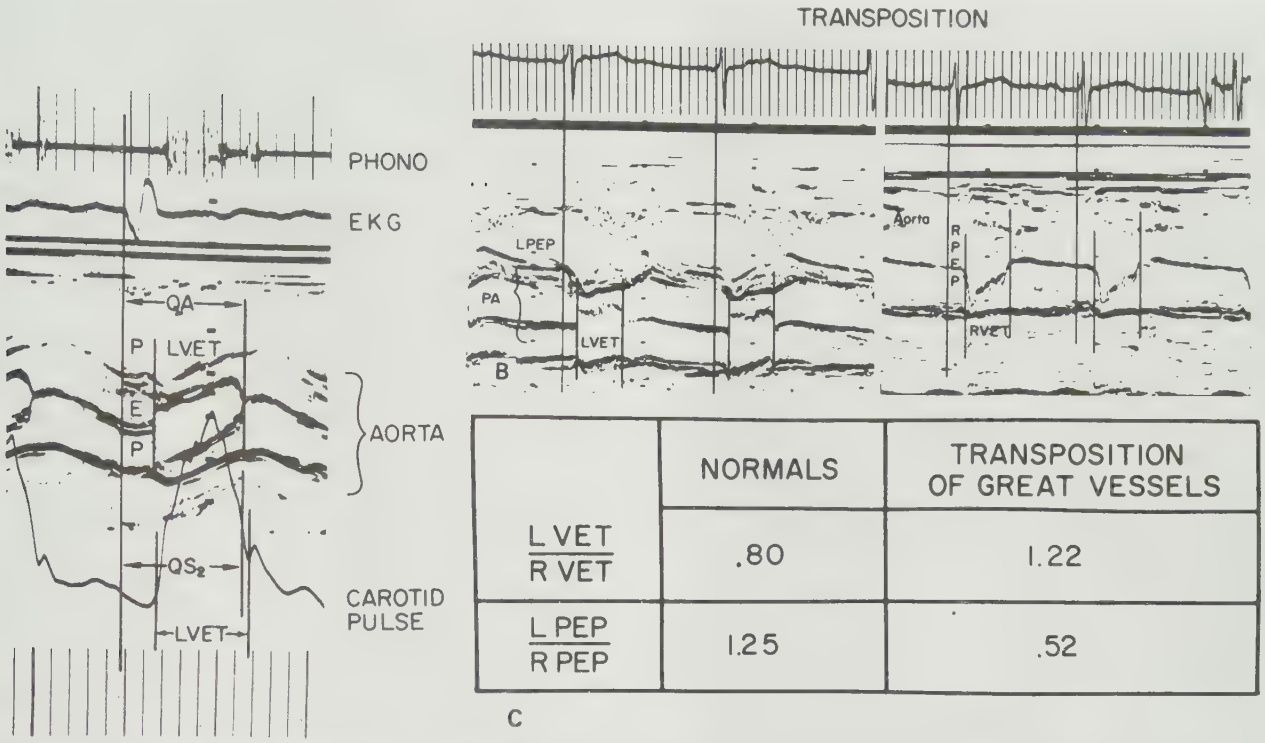
The temporal resolution of two-dimensional echocardiography is limited by the scanning rate limits of the equipment. M-mode techniques interrogate the heart at a much higher rate (800 to 1500 times per second) and allow tracking of the ventricular wall and valves at rapid rates of movement. Factors such as the rapidity of the pulse repetition frequency and the depth of the scan alter the maximum rate of ultrasonic sampling. M-mode echocardiography has been used for the diagnosis of congenital heart defects in the past,[36] however, it has been completely supplanted by two-dimensional imaging for this purpose. The most useful application of M-mode echocardiography is the measurement of absolute cardiac chamber dimensions and wall thicknesses and their dynamic changes. Normal values for the systolic and diastolic dimensions of the left atrium and ventricle increase with increasing age and body size. M-mode parameters from the left ventricle can be used to estimate the wall stress of the left ventricle and its dynamic changes. Systolic function can be estimated using the concept of shortening fraction. In the presence of normovolemia, the dimensional shortening of the left ventricular endocardial cavity relates well to the stroke volume.

The first attempts at noninvasive measurement of pulmonary artery pressure were made possible by M-mode echocardiography. Systolic time intervals of the pulmonary valve (preejection period divided by the ejection time) (Fig. 46–27) correlate with the peak systolic pulmonary artery pressure.[37] In transposition of the great arteries, the pulmonary artery pressure can be estimated by the systolic intervals of the left ventricle.[38]

Changes in the pattern of the opening of the pulmonary valve on M-mode were used to detect pulmonary stenosis[39] but have been supplanted by Doppler techniques (see Chapter 47).

CONTRAST ECHOCARDIOGRAPHY

An ultrasonic contrast agent is a substance with stable microbubbles in solution; these microbubbles are large enough to reflect ultrasound but small enough that they disappear rapidly and are safe.[40] Such an agent may be as simple as saline or as complex as precision engineered microbubbles of polysaccharide that dissolve in the circulation after injection. A contrast injection can be useful in defining the identity of a structure that is imaged but may be unusual.[41] For example, a structure near the aortic arch may be confusing but can be confirmed to be the innominate vein by an echocardiographic contrast injection in a left arm vein (Fig. 46–28). In congenital heart disease the major application of contrast echocardiography is in the postoperative patient with residual shunts or in excluding congenital heart disease.[42] Systemic venous injection of contrast fills the right heart sequentially and the site of residual right-to-left shunting can be defined.[43] A catheter can be advanced retrogradely into the left ventricle after closure of a ventricular septal defect and a contrast injection can be used to diagnose the presence and severity of residual left-to-right shunts. There are concerns about the use of new agents designed to enter the left heart circulation and their effect on developing children.



	NORMALS	TRANSPOSITION OF GREAT VESSELS
$\frac{\text{L VET}}{\text{R VET}}$	.80	1.22
$\frac{\text{L PEP}}{\text{R PEP}}$	1.25	.52

C

Fig. 46–27. (A) Recording of the echocardiogram, phonocardiogram (PHONO), electrocardiogram (EKG) and carotid pulse illustrates the systolic time intervals derived from echo and carotid pulse tracing at paper speed of 125 millimeters per second. (B) The echocardiogram of a patient with transposition of the great vessels demonstrates the systolic time intervals (STI) in normal patients and patients with transposition of the great arteries. LPEP = left preejection period; LVET = left ventricular ejection time; PA = pulmonary artery; PEP = preejection period; QA = electromechanical systole by echo; QS2 = electromechanical systole by carotid pulse tracing; RPEP = right preejection period; RVET = right ventricular ejection time. (Reproduced with permission from Hirschfeld, S., et al.: Measurement of right and left ventricular systolic time intervals by echocardiography. Circulation, *51*:304, 1975.)

SAFETY OF ULTRASOUND—TWO-DIMENSIONAL/ M-MODE

At the present time, significant adverse effects from the use of ultrasound for imaging or M-mode evaluation have not been reported. The potentially negative bioeffects of ultrasound can be classified into those caused by cavitation and those from heating. Cavitation refers to the development of tiny gas-filled bubbles that resonate at the ultrasonic frequency and induce neighboring particles of liquid to vibrate, thereby potentially damaging the ultrasound-transmitting medium. Practically, the intensities now used (typically 10 Watts per centimeter squared) are nearly an order of magnitude less than those known to produce cavitation. Thermal effects could result from heat generated in the tissue. In order to reach the thermal threshold for damage using modern ultrasonic intensities for imaging and M-mode, an average intensity of 1000 Watts per centimeter squared (100 times the usual intensity) would be necessary for many hours.[29]

The evidence thus far supports the statement that diagnostic ultrasound used at current pulse intensity levels does not constitute a risk or hazard to the patient. Higher intensities with pulsed Doppler have the potential to cause cavitation, and concerns about the use of Doppler in the fetus are currently being investigated.

COST AND BENEFITS

One of the major reasons that ultrasound is proliferating so rapidly in pediatrics is that it is noninvasive. Ultrasound equipment is less expensive than x-ray equipment, for example, and there is a natural process of reassessment going on now of the indications for cardiac catheterization. The development of echocardiography as an extension of the clinician's other assessment skills has led to some decrease in utilization of the catheterization laboratory, especially in neonates. If a catheterization can be completely avoided, then echocardiography has the potential to decrease the cost of medical care for these patients.

For the most effective application of ultrasound in the cardiovascular system, the involvement of a physician during performance of the study, as well as in the interpretation, is important. A more physician-intensive diagnostic process may benefit the patient, but may become more expensive than a test involving only a technician.

FUTURE DIRECTIONS

Technology has been changing so rapidly in this area that it is difficult to predict which technique will be optimal for a given lesion in five years time. The rapid development of nuclear magnetic resonance for imaging and spectroscopy will have a major impact on the field (see Chapter 51). Echocardiography is advancing at a rapid pace. The emerging areas include 1) the development of contrast agents some of which will allow myocardial blood flow assessment by ultrasonography, 2) tissue characteri-

Fig. 46–28. Contrast ultrasonography with injection in a left arm vein during coronal scanning of the anomalous innominate vein. Before (upper panel) and after (lower panel) injection shows opacification of the anomalous vein. (Reproduced with permission from Huhta, J.C.: Pediatric Imaging/Doppler Ultrasound of the Chest. Philadelphia, Lea & Febiger, 1986, p. 182.)

zation techniques, 3) color Doppler blood flow measurement, 4) invasive ultrasonic imaging probes for intracardiac imaging, 5) transesophageal ultrasonic imaging in neonates for intraoperative functional assessment, and 6) three-dimensional reconstruction of cardiac images from ultrasound data. One thing is certain: a nearly constant re-evaluation of the relative roles of various diagnostic modalities in congenital heart disease will be needed.

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CHAPTER 47

Doppler Echocardiography

Daniel J Murphy, Jr

Although Doppler ultrasound was developed prior to M-mode and two-dimensional echocardiography, its use remained limited prior to the late 1970s. At that point, newly introduced systems combined two-dimensional imaging with pulsed Doppler ultrasound. This use of two-dimensional echocardiography (2DE) as a guide for the placement of a Doppler sample volume allowed confirmation of findings previously made by "blind" continuous wave and pulsed Doppler ultrasound; 2DE also simplified the examination of individual locations within the vascular system and paved the way for Doppler ultrasound to become an integral part of the echocardiographic evaluation. Whereas 2DE is used to obtain information regarding the structure of the heart, Doppler is used to detect the disturbances in flow that result from abnormalities of structure. In addition, Doppler augments the M-mode and two-dimensional evaluation of systolic and diastolic function. Finally, through the use of Doppler, it is possible to estimate intracardiac pressure gradients and flow areas.

The goals of the Doppler echocardiographic examination are: 1) to document the presence of normal flow patterns; 2) to detect the presence of flow disturbances or abnormal patterns; 3) to measure the velocity of flow at each point within the vascular system; and 4) to estimate the flow volume at each point in the heart and great vessels. Although not all of these aspects are necessarily addressed during each examination, they represent the potential information available on each occasion.

In general, the Doppler echocardiographic examination should be complementary to a complete 2DE evaluation. The segmental anatomy and the intracardiac and extracardiac connections should be established prior to Doppler interrogation. Once the structural information is obtained, a complete Doppler examination at each location within the great vessels or intracardiac chambers should be performed. Information is obtained regarding the pattern of blood flow, the velocity of blood flow, and the volume of blood flow. These data can be obtained using pulsed Doppler, continuous wave Doppler, or two-dimensional color Doppler. It is advisable to use single sample volume pulsed Doppler or color Doppler for routine screening at various sites. Continuous wave Doppler is generally reserved for determination of peak velocities when aliasing or flow disturbance is noted on the pulsed Doppler display.

TYPES OF DOPPLER EQUIPMENT

Doppler echocardiography is generally performed using one of three formats: 1) pulsed Doppler; 2) continuous wave Doppler, and 3) two-dimensional color Doppler. Doppler equipment includes the transducer, the signal processing unit, and the information outputs. Doppler instrumentation can be free-standing—that is, without any other echocardiographic imaging capability—or it can be part of an ultrasound system that contains other ultrasonic features such as two-dimensional imaging or other Doppler formats.

The configuration of Doppler transducers depends on the type of Doppler and whether the system is shared with an imaging system. Single crystal nonimaging transducers are compact with a small contact face. Such transducers are particularly useful for accessing small ultrasound windows such as intercostal spaces or the suprasternal notch. Transducers that function for imaging and Doppler are larger and available in a variety of configurations (Fig. 47–1). The ultrasound beam may emerge in line with the

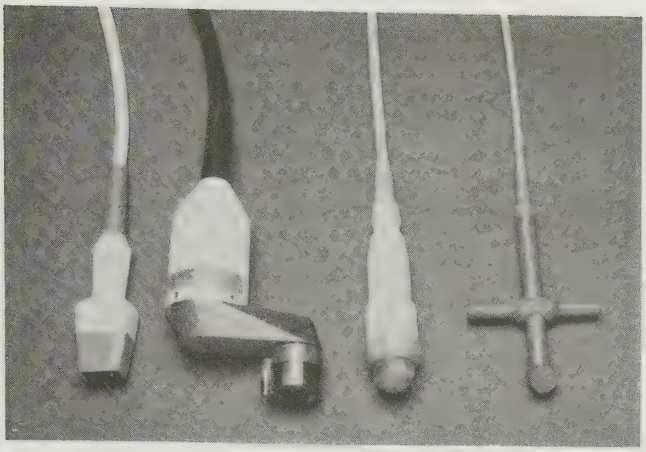

Fig. 47–1. Doppler echocardiographic transducer configurations. From left to right, the following types of transducers are pictured: 1) a phased array transducer that combines imaging with pulsed and continuous wave Doppler; 2) a mechanical sector scanner that combines imaging with pulsed and high-pulse repetition frequency Doppler; and 3) an annular array transducer that combines imaging with pulsed, high-pulse repetition frequency pulsed, continuous wave, and color Doppler. Finally, the transducer to the right is a nonimaging transducer with pulsed and continuous wave capability.

axis of the transducer, or it may be offset by as much as 90° to facilitate access to particular areas. Each transducer has a different "footprint"—that is, the ultrasound beam emerges with a specific width and orientation. Difficulties in imaging or Doppler interrogation may be alleviated by changing to a transducer of a different configuration.

Pulsed Doppler capability is available now on nearly all 2DE machines. In addition, color Doppler and continuous wave Doppler are available on many systems with linear, phased, or annular array systems. Another difference among the imaging systems with Doppler is related to the ability to direct the Doppler beam using the two-dimensional image for guidance. Some systems have a fixed Doppler path, and the operator must angle the scan plane so that the Doppler beam intersects the area of interest. With steerable Doppler systems, the Doppler beam can be maneuvered by means of a joystick or trackball into the desired location.

DOPPLER SIGNAL PROCESSING

Doppler ultrasound units employ a variety of signal processing methods (see Chapter 36). While the simplest Doppler units produce only an audio signal, most systems designed for examination of the heart and great vessels use a more sophisticated form of signal processing in an attempt to display information regarding the velocities encountered. The older and simpler units used zero crossing counters to produce a time-interval histogram. However, these units have been replaced by those containing fast Fourier transform analysis units. Even among systems with FFT capability, there are differences in sampling rate. Faster sampling rates allow for less time delay between signal acquisition and display. They also produce more reliable point-to-point temporal resolution of recorded velocities.

All Doppler units have an audio output. This is due in part to the fact that the Doppler frequency shifts produced by blood flowing at physiologic velocities are in the audible range. Most ultrasonographers rely on the characteristics of the audio signal for information regarding the nature and velocity of the flow. For example, higher-pitched sounds indicate faster blood velocities. An audio signal with a pure tone (a whistling sound) indicates a narrow band of velocities suggesting laminar flow. Conversely, areas of disturbed flow contain a range of velocity components, and the resultant audio signal has a harsh quality.

In addition to the audio output, spectral information from the Doppler interrogation is generally displayed on a video screen as a time-velocity plot. By convention, signal produced by flow toward the transducer is displayed above the zero line and flow away is displayed below. An ECG trace is usually present on the display and allows timing of Doppler signals in relation to the cardiac cycle.

As well as the video display, Doppler output is often available in a hardcopy or paper format. This can be a stripchart recorder or a video screen page printer. Frequently, the Doppler output provides information regarding the specific conditions under which the Doppler system is operating. These parameters include calibration lines for velocity and time, sample volume size and carrier frequency of the transmitted ultrasound beam, depth of sampling, and wall filter settings. Each of these factors is important in obtaining the best possible Doppler recording.

With a wide variety of Doppler echocardiographic equipment available, there is no simple answer to the question "which echocardiographic equipment is appropriate for one's clinical needs." In fact, the simplest generalization is that no echocardiographic equipment with or without Doppler capability is perfect for every situation. For this reason, many clinical noninvasive imaging laboratories are equipped with several ultrasound systems with different features. The strength of any diagnostic ultrasound system should be its imaging capability. Structural diagnosis is the centerpoint of echocardiographic evaluation. Some systems with high frequency (7.5 to 10 MHz) transducers are exceptional for their ability to image the heart of the premature or newborn infant. However, the same system may be inadequate for examining larger patients. Conversely, many phased-array systems have either poor near-field resolution or a transducer shape that is inappropriate for a small infant.

Any echocardiographic system should include high-quality pulsed and continuous wave Doppler. Both should be steerable using the two-dimensional image. Standard features include a variable size sample volume and high pulsed repetition frequency on the pulsed Doppler. In addition, the audio quality of the signal should be adequate to allow the examiner to incorporate it into the interpretation of the examination.

Color Doppler is rapidly becoming an integral part of the Doppler examination and should be available in every pediatric echocardiographic laboratory. However, not every ultrasound system in the laboratory must include color Doppler. There is also a need for smaller systems with excellent imaging, pulsed Doppler, and continuous wave Doppler. When purchasing equipment that includes color Doppler, one must not sacrifice image quality or the quality of pulsed and continuous wave Doppler for the sake of the color display. Current color systems are evolving rapidly. Therefore, another desirable feature is that the system be upgradable as new advances are made. Any system is more desirable if hardware or software changes can be made to improve it or add new features to the existing color display.

Hardcopy format is desirable on all echocardiographic systems.

Any systems with color Doppler should be equipped with a color printer or Polaroid camera. A black-and-white page printer or stripchart recorder is also essential.

When purchasing an ultrasound system, one must get transducers that provide adequate imaging and Doppler for the range of patients to be studied. In a pediatric laboratory, this frequently includes the entire range of available transmission frequencies from 2.25 MHz to 7.5 MHz. It also may include probes with different types of crystals (e.g., phased array, annular array, and single crystal continuous wave Doppler).

Finally, when purchasing any new echocardiographic equipment, one should consider the availability of trained service personnel. New systems have become increasingly complex and technologically sophisticated. That, coupled with the increasing clinical dependence placed upon echocardiographic information, makes the reliability and serviceability of any echocardiographic system crucial.

Doppler Signals

Doppler information is produced as a spectral display and as an audio signal, and the examiner must interpret the output and relate it to the qualities of the area of blood flow being examined. First, the Doppler signal identifies the presence of flow. With the exception of low-frequency wall-motion artifacts and higher-frequency valve clicks, the presence of any Doppler signal indicates blood flow. The absence of Doppler output does not necessarily imply the absence of flow. Rather, it might result from a technical problem in the performance or the analysis of the examination. For example, placement of the sample volume outside the vascular system will not produce a Doppler signal. This can occur when the operator activates the Doppler apparatus but does not update the sample volume position using the two-dimensional image. More commonly, lack of Doppler signal results from an attempt to sample at too great a depth, with a high-frequency transducer, or with inadequate or improper power and/or gain settings.

Normal Flow

Once flow has been detected, the direction of flow is assessed. Flow toward the transducer is displayed above the zero line, and flow away from the transducer is displayed below. If the ultrasound beam is aligned relatively perpendicular to the axis of flow, flow will either appear to be of low velocity or bidirectional. Another cause for apparent bidirectional flow is spectral mirroring, which occurs when the Doppler gain settings are inappropriately high. Doppler sampling in a stream with laminar flow will produce a spectral pattern with a narrow range of frequencies throughout the period of flow. Movement of the sample volume toward a vessel wall where viscous drag results in broader range of velocities will also result in a wider Doppler display. This phenomenon is referred to as "spectral broadening." The Doppler patterns then depend on the nature of the blood flow in the area sampled, the size and location of the sample volume, and the precise adjustments and settings of the Doppler apparatus. A thorough familiarity with the normal patterns is essential before one can confidently recognize and identify the cause of abnormal patterns.

Disturbed Flow

Disturbed flow and turbulence are easily recognized and distinguished from normal laminar flow by their Doppler signals. Flow disturbance results in a change in direction of many of the blood cells in the stream of flow. This changes the angle between the path of the individual cells and the ultrasound beam, resulting in a change in the apparent velocity components. Interrogation of an area in which individual blood cells are moving in a number of different directions results in a spectral output that contains a wide range of velocities at that particular instant. The Doppler output appears wider due to spectral broadening. As the flow disturbance becomes more severe, spectral broadening becomes more pronounced and velocity components may be observed moving both toward and away from the transducer simultaneously (Fig. 47–2). Disturbed flow alters the color Doppler output as well. Spectral broadening results in a greater variance in the sampled frequencies, producing a green or yellow color on the display.

Flow through a stenotic valve has a characteristic pattern (see Chapter 34). There is acceleration of the blood immediately proximal to the obstruction. Flow through the obstruction itself occurs as a high-velocity laminar jet. However, this laminar quality to the flow is immediately lost as the poststenotic eddies and vortices develop in the poststenotic region. Doppler sampling proximal to, in, and distal to the obstruction will reveal each of the components of this flow disturbance.[1–3]

THE DOPPLER EXAMINATION

The Doppler examination generally is performed as an integral part of a complete echocardiographic evaluation. As with any echocardiographic examination, it is advisable to examine all cardiac structures, and each Doppler examination should be as complete as possible. The Doppler examination may require from 5 to 60 minutes to perform; the patient must be comfortable and clinically stable. In addition, a fairly constant heart rate is useful. In the case of infants and small children, it may be necessary to perform the study during sleep or with the use of a sedative. Agitation not only makes the examination difficult but can also result in erroneous information due to improper sample volume location and patient motion during the examination. Flow velocities across both normal and stenotic valves differ between the awake and sedated states.[4,5]

The specific order in which the Doppler examination is performed is unimportant. In addition, it does not matter whether the 2DE examination is performed before or after the Doppler study. However, the two-dimensional information must be integrated with the Doppler assessment into an overall diagnostic picture. Frequently, this means that after an initial assessment, the study is reviewed and the need for further information is noted. Therefore, it is not unusual for more than one two-dimensional and Doppler examination to be performed on the same patient before complete diagnostic information is available.

Several strategies are acceptable for pursuing the Doppler examination. One is a "view-oriented approach," through which Doppler information is obtained in each of the standard echocardiographic views. This has the advantage of shortening the examination and does not require frequent repositioning of the patient. It has the disadvantage that blood flow is sampled at the same time in a variety of locations unrelated to each other. The examiner must mentally catalog the information as it is obtained and unify it at the end of the examination. An alternative approach is to sample flow in a physiologic fashion—that is, to follow the

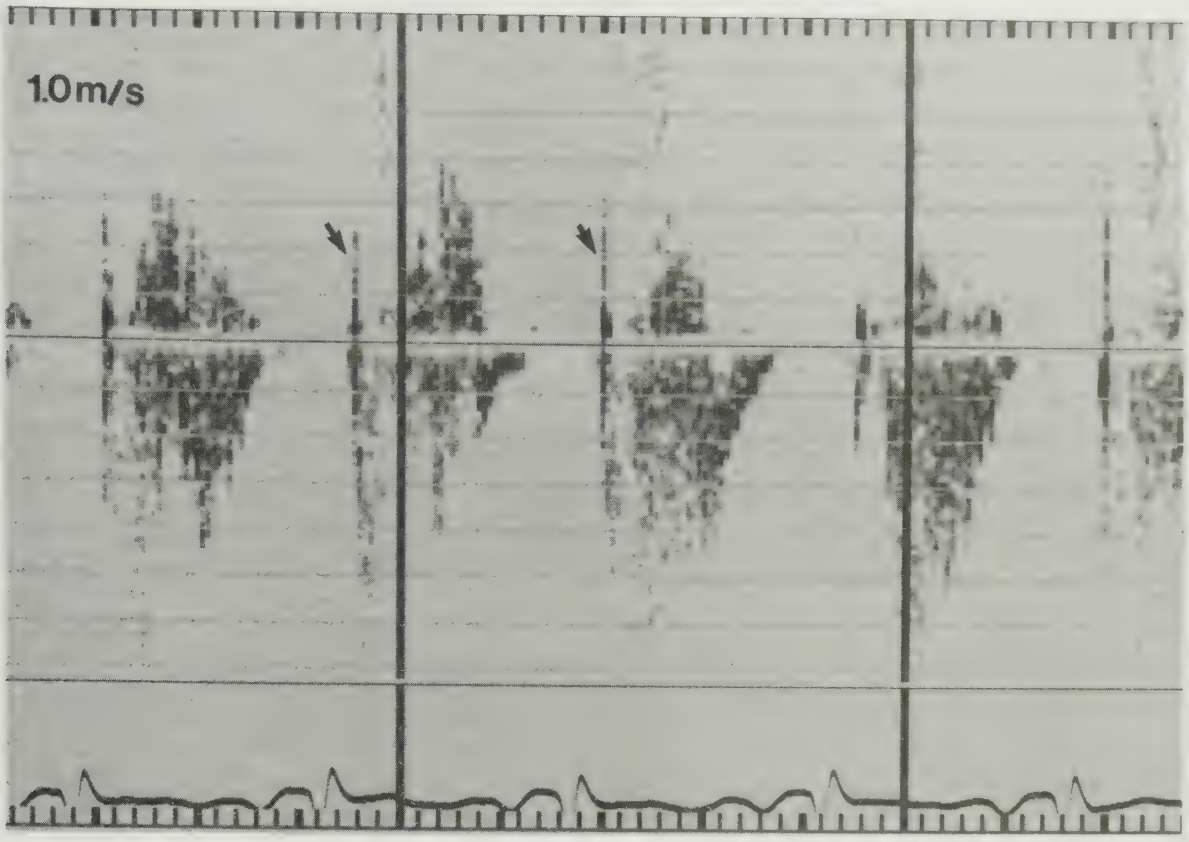

Fig. 47–2. Disturbed flow. A pulsed Doppler sample volume has been placed in the main pulmonary artery just distal to the valves. Doppler signals from valve opening are noted (arrows). The Doppler flow pattern consists of a wide range of velocity components. The occurrence of signals above and below the zero line suggests flow in multiple directions. This is due to the presence of eddies in the parajet flow disturbance.

venous flow as it enters the heart and sequentially sample flow patterns following the flow of blood through the right side and then the left side of the heart. This approach is somewhat inconvenient and impractical. However, the concept is sound and forces the examiner to acquire Doppler information at all possible sites.

What type of Doppler should be used in a routine examination? In general, pulsed Doppler should be used for the detection of flow disturbances and for the measurement of velocities within the normal range. This can be done either with single sample volume pulsed Doppler or with color Doppler display. Using the single sample volume equipment, the sample volume must be moved sequentially from one area of the heart to the other during recording of the Doppler output. This approach is somewhat tedious and time-consuming. However, done carefully it is exquisitely sensitive and provides a large amount of information. Theoretically, the same capability exists using color Doppler; color Doppler shortens the examination time by allowing the examiner to view larger areas of Doppler information simultaneously. Early generation color Doppler systems had poor sensitivity and low pulse repetition frequency. Thus, it was possible to miss small flow disturbances or areas of low flow velocity. This was particularly true in children with fast heart rates or in adults at a greater depth of sampling. As the quality of color Doppler systems improves, it is likely that this will become the modality of choice for routine Doppler screening examination. Using these systems, one sequentially interrogates each area of the heart from a variety of views looking for the presence of high-velocity flows or areas of disturbed flow. Continuous wave Doppler is generally reserved for the examination of areas with higher-flow velocity or a great distance from the transducer. It is most useful to perform continuous wave Doppler sampling after prior pulsed or color Doppler examination.

Goals

The Doppler examination is intended to characterize flow in each of the cardiac chambers as well as in the great vessels. This allows the detection of any flow disturbance. In addition, the complete Doppler examination includes estimation of flow velocity in each of the locations sampled and, frequently, estimation or calculation of flow volume in certain sites. This information is obtained from a variety of echocardiographic windows at various times during the patient examination. In fact, it is advisable to interrogate each area of interest from as many windows as possible. It is also useful to identify structural abnormalities using two-dimensional imaging prior to the performance of the Doppler examination. This alerts the examiner to areas which require special attention during the Doppler examination. In the following sections, flow patterns are described following the pathway of blood flow into and through the heart.

Systemic Venous Flow

The pattern of systemic venous flow is biphasic. There is a portion of venous flow that occurs during ventricular systole (atrial filling). This is followed by a second period of flow during atrial diastole (following atrial contraction) (Fig. 47–3). Flow velocities range from 30 to 80 cm per second, and there is generally a noticeable respiratory variation with increased velocities occurring during inspiration.[6]

Abnormalities of venous flow can be characterized by: 1) increased flow volume and velocity (increased flow due to anomalous pulmonary venous return[7] or arteriovenous malformations); 2) increased velocity, flow disturbance, and loss of normal phasic pattern due to stenosis, which could be due to obstruction of the veins themselves or due to obstruction due to a baffle following intra-atrial correction of transposition of the great arteries; and 3) flow reversal during systole due to tricuspid regurgitation[8,9] or restrictive ventricular physiology.[10]

Flow in the superior vena cava is examined best from the suprasternal notch. From this window, blood flows away from the transducer. The subcostal window can also be used. Flow in the inferior vena cava should be examined from the subcostal location.

Right Atrium

Normal flow in the right atrium represents a convergence of flow from the superior vena cava and the inferior vena cava.[11] As flow approaches the tricuspid valve, the velocities increase slightly but retain the biphasic pattern: there is a prominent early filling phase during early diastole and a less pronounced late filling phase following atrial contraction.

Normal flows in the right atrium can be disturbed by additional flow entering through an atrial septal defect,[12,13] or from anomalous pulmonary venous drainage[7,14] by a systolic jet from tricuspid regurgitation.

Flow in the right atrium is best examined from the apical or subcostal windows. Normally, all flow occurs toward the transducer from these locations. Any flow detected away from the transducer likely represents tricuspid regurgitation.[15,16] The distinction between normal flow and flow through an atrial septal defect can be difficult. This is due to the fact that flow normally occurs along the atrial septum from the inflow of the superior vena cava. Separation of the two streams of flow is most easily accomplished with the use of color Doppler.[17–21]

Tricuspid Valve and Right Ventricular Inflow

The biphasic flow into the right ventricle produces a characteristic M-shaped pattern on the Doppler tracing. The early filling phase occurs during early diastole; then, velocities are slightly higher and volumes are slightly larger than during the late filling phase (Fig. 47–4). Normal velocities range from 30 to 80 cm per second. Abnormalities of tricuspid inflow include: 1) increased velocity due to increased venous return or left-to-right shunt at the atrial level; 2) increased velocities and flow disturbance due

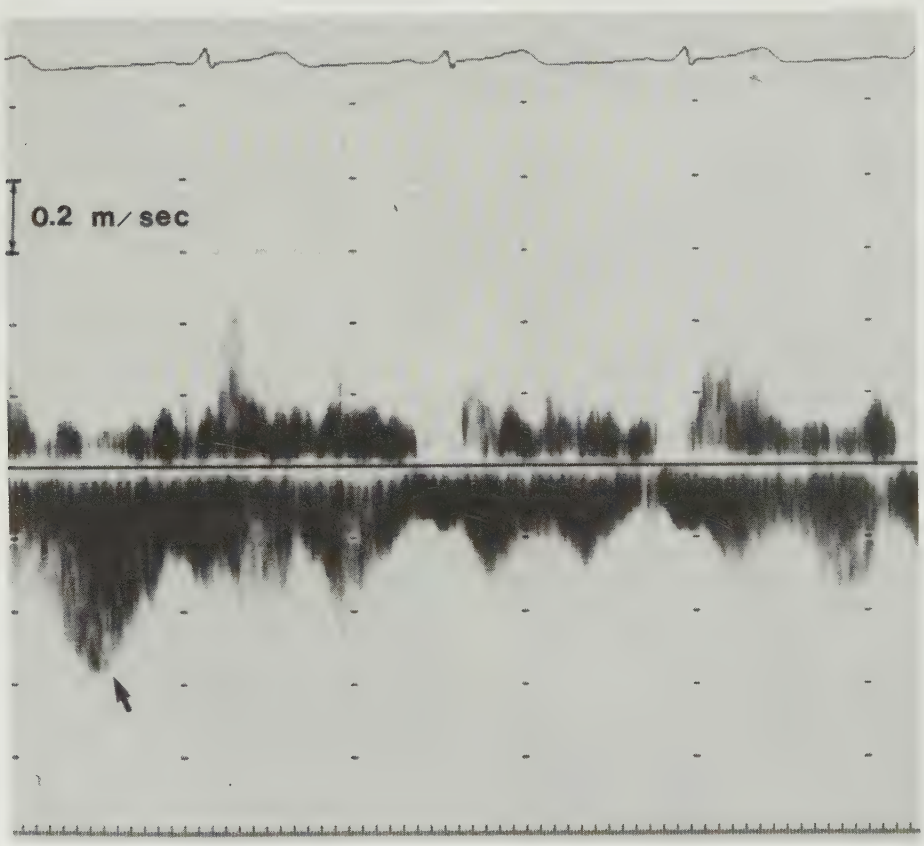

Fig. 47–3. Flow in the superior vena cava. Venous inflow is typically biphasic with a prominent systolic component followed by an early diastolic phase. In the superior vena cava, flow is also affected by the respiratory cycle with an accentuation of inflow during inspiration (arrow).

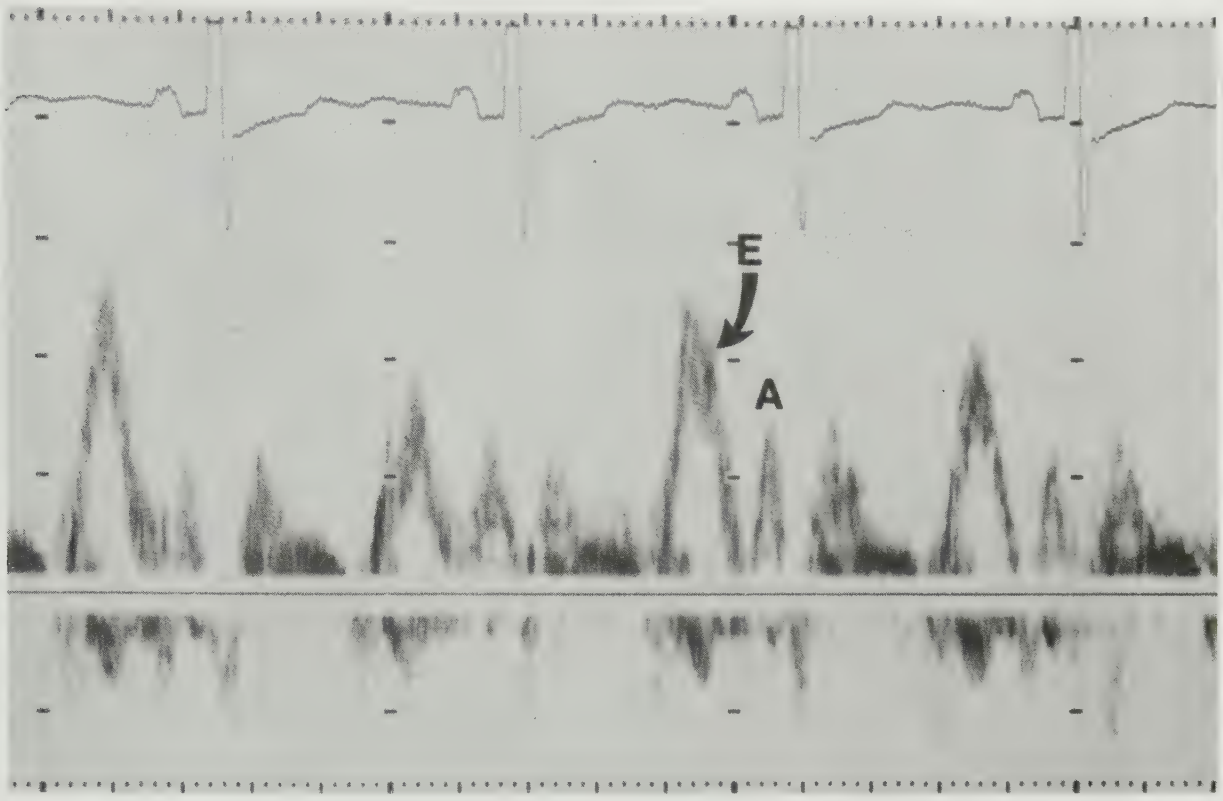

Fig. 47–4. Normal tricuspid inflow. Tricuspid inflow has a biphasic pattern with a prominent early filling phase (E) and a less prominent late filling phase that follows atrial contraction (A). Tricuspid inflow velocities and time velocity integrals vary with position and respiratory cycle.

to tricuspid stenosis; and 3) systolic flow reversal due to tricuspid regurgitation. Flow reversal must be holosystolic to establish the presence of true tricuspid regurgitation.[16] Short, early systolic flow reversal occurs in normal individuals.[22] This jet is not pathologic, but can be useful in estimating right ventricular pressure.

Flow through the tricuspid valve and into the right ventricle is best sampled from the apical window. An alternative is to sample the right ventricular inflow from the parasternal window.

Right Ventricular Outflow and Pulmonary Valve

Flow in the right ventricular outflow tract occurs primarily during systole, although some low-velocity forward flow can be detected in diastole.[23] Flow is laminar and produces a clean systolic signal with velocities ranging from 40 to 100 cm/second. As the sample volume is moved into the pulmonary valve region, valve clicks are detected on the Doppler tracing and the audio signal. A normal pulmonary artery Doppler signal has a rounded contour with the peak velocity occurring in midsystole. Normally, there is no forward diastolic flow detectable in the right ventricular outflow tract or main pulmonary artery. However, an early diastolic signal produced by trivial pulmonary regurgitation is commonly present in normal individuals (Fig. 47–5).[15,22,24]

A variety of structural lesions can account for flow disturbances in the right ventricular outflow tract. Perimembranous and muscular ventricular septal defects are accompanied by jets from left ventricle to right ventricle that produce flow disturbances in the right ventricular outflow tract (Fig. 47–6). Such jets are usually holosystolic[25–28] and are easily identified on color Doppler examination.[18,19,21,29–31] The orientation of the jet depends on the location of the defect. Anomalous muscle bundles such as those in double chamber right ventricle, tumor,[32,33] and aneurysm of the ventricular septum[34] can all produce flow disturbances in the right ventricular outflow tract. Infundibular pulmonary stenosis also results in an acceleration of blood and a flow disturbance proximal to the pulmonary valve. In pulmonary valve stenosis, there is a slight acceleration of blood immediately proximal to the valve, but the Doppler pattern is undisturbed until the sample volume is moved distal to the valve leaflets themselves. True pulmonary regurgitation produces a Doppler signal throughout diastole and is detectable more than several millimeters proximal to the valve leaflets.[22] In addition to flow disturbances caused by structural disturbances, it is also possible for flow velocities to be increased in any situation in which return to the right heart is abnormally high. Therefore, conditions such as atrial septal defect or increased cardiac output may produce increased velocities for other reasons. Only rarely will such conditions lead to flow disturbances.

Flow in the right ventricular outflow tract and main pulmonary artery can be sampled from the parasternal window in the short axis view or from the subcostal location. The parasternal location has the advantage of placing the transducer closer to the right ventricular outflow tract. However, the Doppler sample volume is better aligned with the axis of flow from the subxiphoid position. Therefore, qualitative studies particularly using color Doppler may yield more information from the parasternal window[35] whereas the maximal peak velocity may be obtained from another transducer position.[36]

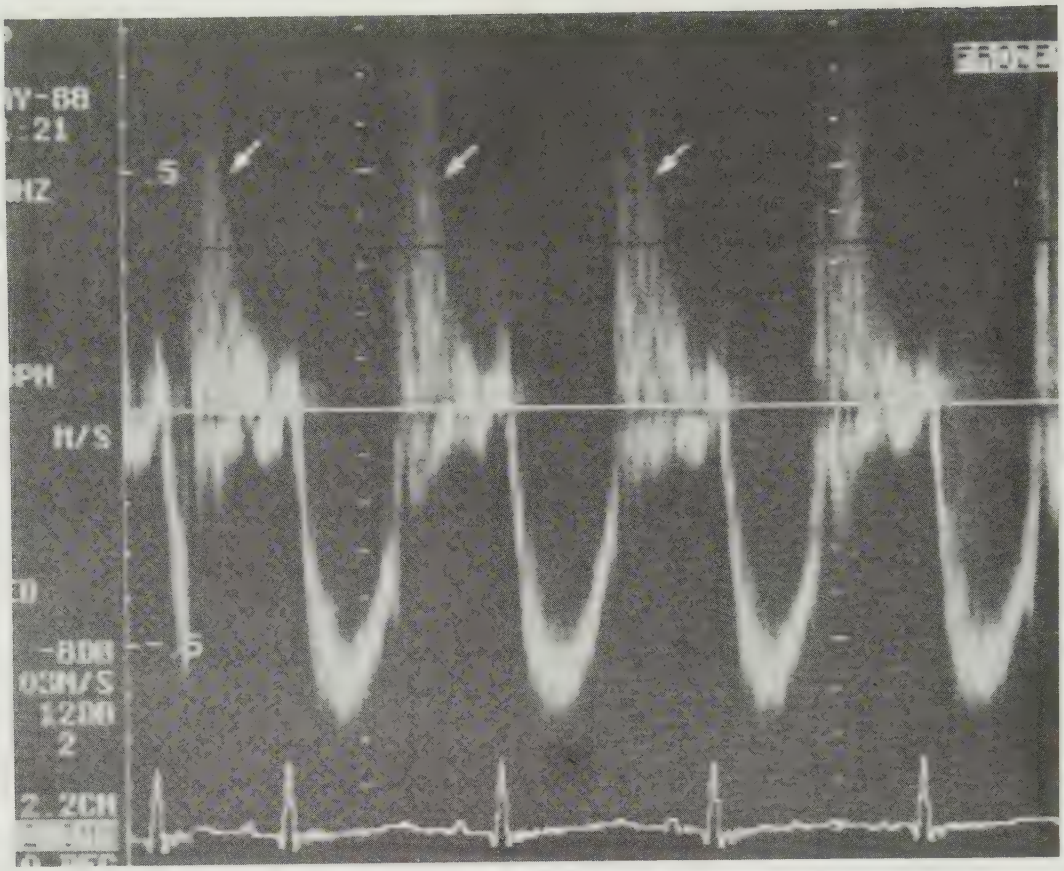

Fig. 47–5. Normal pulmonary flow with pulmonary regurgitation. The sample volume is placed in the main pulmonary artery at the level of the pulmonary valve. Flow occurs during systole away from the transducer (downward), and a narrow envelope is present. Compared to aortic flow, pulmonary peak velocity occurs during midsystole with a more gradual acceleration. In this tracing, mild pulmonary regurgitation is present (arrows) that appears as diastolic flow toward the transducer. This pattern of pulmonary regurgitation is normal particularly when detected close to the pulmonary valve leaflets.

Pulmonary Arteries

Flow in the pulmonary arteries occurs normally only during systole with the exception of low velocity early and late diastolic forward flows related to right ventricular filling and atrial contraction[37] and low velocity diastolic forward flow in the distal pulmonary arteries. Whereas normal velocities in the main pulmonary artery rarely exceed 120 cm/sec, normal velocities in the left pulmonary artery are considerably higher. In the newborn infant, the left and right pulmonary arteries are small compared to the main pulmonary artery, and blood accelerates as it enters the branch pulmonary arteries. This phenomenon, which is responsible for the physiologic murmur of peripheral pulmonary stenosis in such infants, can result in systolic velocities as high as 220 cm/sec, and may cause continuation of flow into diastole in the pulmonary artery branches.

Flow disturbances in the pulmonary artery can be due to stenosis at or above the pulmonary valve. In addition, proximal flow disturbances (e.g., those produced by ventricular septal defects or infundibular pulmonary stenosis) can be transmitted downstream and result in disturbed flow well into the branch pulmonary arteries. True peripheral pulmonary stenosis produces a pattern of undisturbed flow in the main pulmonary artery with acceleration and flow disturbance in one or both of the branches.[38] Additional sources of flow disturbance in the pulmonary arteries include flow reversal due to severe pulmonary regurgitation and diastolic flow due to left-to-right shunting from an aortopulmonary window, patent ductus arteriosus,[21,39–46] surgically created systemic to pulmonary artery shunt,[47,48] or anomalous coronary artery originating from the pulmonary artery.[49] The source of any of these flow disturbances can be identified by careful two-dimensional imaging as well as Doppler interrogation of the pulmonary artery to detect a point of flow entry. Pulsed,[39,40,43] continuous wave,[45] and color Doppler[19,21,50] have increased the sensitivity of echocardiographic identification of patent ductus arteriosus (Fig. 47–7).

Doppler sampling in the main and left pulmonary arteries is best performed from the subcostal location. Sampling in the right pulmonary artery can be performed from the parasternal or suprasternal view. Unfortunately, from these locations the Doppler sample volume is aligned nearly perpendicular to the direction of flow, and good Doppler records are difficult to obtain. Color Doppler can frequently be used from the suprasternal notch to detect a flow disturbance in the right pulmonary artery.

Pulmonary Venous Return

Pulmonary venous flow produces a pattern similar to that seen in systemic veins. It is biphasic with an early phase during systole

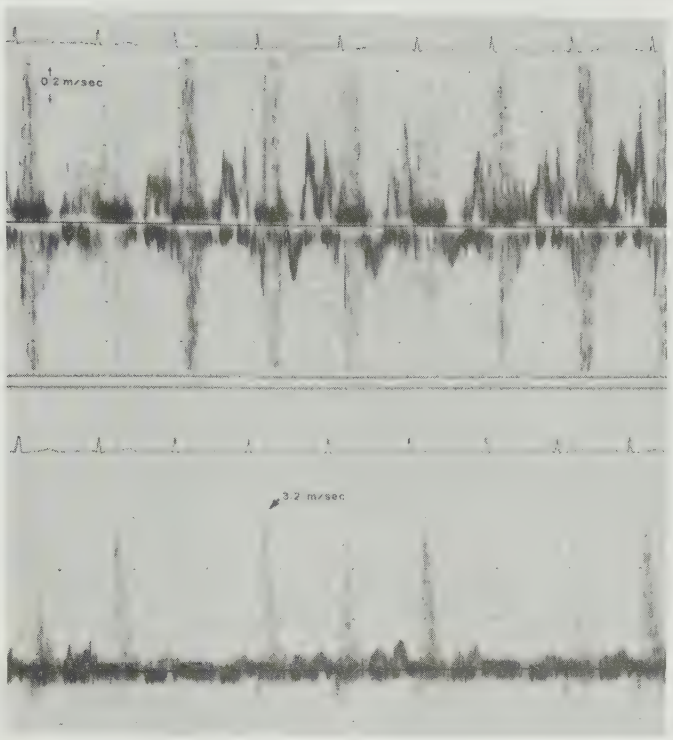

Fig. 47–6. Ventricular septal defect. In the upper panel, a pulsed Doppler sample volume is placed in the right ventricular inflow tract. Normal tricuspid inflow pattern is present during diastole. During systole, there is a signal of disturbed flow that exceeds the Nyquist limit. Flow occurs throughout systole. In the lower panel, a continuous wave beam has been directed toward the area of flow disturbance. A high-velocity systolic jet is present. Flow toward the transducer produces the Doppler signal above the zero line.

and a second phase in diastole.[51–53] Pulmonary venous flow is somewhat less affected by respiratory variation. Normal pulmonary venous velocities range from 20 to 80 cm/sec. Doppler tracings with velocities in excess of 2 m/sec, particularly if accompanied by a loss of the normal phasic pattern,[53–55] suggest pulmonary venous obstruction. Pulmonary venous flow is best sampled from the apical and subcostal windows.

Left Atrium

Flow in the left atrium has a low velocity and is similar to flow in the right atrium. Doppler velocities increase to 40 to 100 cm/sec as sample volume is moved closer to the mitral valve. Disturbances in flow can be produced by right-to-left atrial shunting, obstructed pulmonary venous return (e.g., cor triatriatum or baffle obstruction following intra-atrial correction of transposition of the great arteries),[55] or mitral regurgitation. In the presence of mitral regurgitation, there is holosystolic flow disturbance in the left atrium near the mitral valve leaflets.[56] Color Doppler displays a green or yellow jet that originates at the mitral valve and extends into the left atrium. Attempts have been made to estimate the severity of mitral regurgitation using pulsed Doppler mapping[57–60] or color Doppler jet area.[61–67] These methods are at best a semiquantitative "grading" of severity. Combining mapping with estimates of regurgitant fraction[68,69] may improve accuracy. In normal individuals, a short early systolic signal is detectable in the left atrium immediately adjacent to the mitral valve. This represents a normal finding.[22,56]

Flow in the left atrium is best sampled from the apical window. The mitral valve flow also can be examined using a parasternal long axis view.

Left Ventricular Inflow

As the sample volume is moved into the funnel of the mitral valve, inflow velocities increase, but the Doppler signal retains its characteristic M-shaped pattern (Fig. 49–8). As sampling proceeds toward the apex of the left ventricle, velocities decrease slightly and there is a disturbance of flow due to the eddies normally present at the apex.

The major abnormality detectable in this region is disturbed flow due to mitral stenosis. Mitral stenosis results in increased inflow velocities and a change in the characteristic Doppler pattern. The time of early filling is prolonged because left atrial pressure exceeds left ventricular pressure throughout diastole. Estimation of the severity of mitral stenosis can be made based on the peak velocity of the inflow jet or on the slope of the inflow velocities. Color Doppler examination of normal mitral inflow reveals a homogeneous red signal.[70,71] Mitral stenosis produces a pattern of aliasing and increased variance due to the flow disturbance at the narrowed valve orifice.[35,72] Left ventricular inflow is best sampled from the apical window.

Left Ventricular Outflow

Flow in the left ventricular outflow tract occurs in systole and moves away from the transducer when sampled from the apical window. As the sample volume is moved toward the aortic valve, velocities increase slightly and there is narrowing of the spectral width. At the aortic annulus, the valve leaflets create clicks on the Doppler tracing. As the sample volume is advanced to the proximal aorta, the pattern remains essentially unchanged. Color flow mapping reveals a homogeneous signal during systole throughout the left ventricular outflow tract.[70,73]

The most common lesions that produce flow disturbance in the left ventricular outflow tract are subaortic stenosis, valvar aortic stenosis, and aortic regurgitation (Fig. 47–9). A careful pulsed Doppler examination or a two-dimensional color examination can be useful in localizing the site of flow disturbance. When combined with the anatomic appearance of the left ventricular outflow tract and aortic valve, it simplifies detection of the location of stenosis.[35,74–76] Doppler has also proven useful in the identification and characterization of flow disturbances caused by dynamic subaortic obstruction in hypertrophic cardiomyopathy.[77–81]

The presence of any diastolic flow in the region of the aortic valve is abnormal and likely represents the presence of aortic insufficiency. Other courses of diastolic flow in the left ventricular outflow tract include aortico–left ventricular tunnel.[82,83] Pulsed Doppler and color Doppler are extremely sensitive in the detection of aortic regurgitation.[62,84–87] Careful pulsed Doppler mapping or two-dimensional color flow can be used to examine the location and extent of the regurgitant area. Such mapping correlates well with angiographic grading of severity of aortic regurgitation.[67,88–90] Additional estimates of severity can be obtained by applying the pressure half-time concept to the aortic regurgitation jet.[91,92]

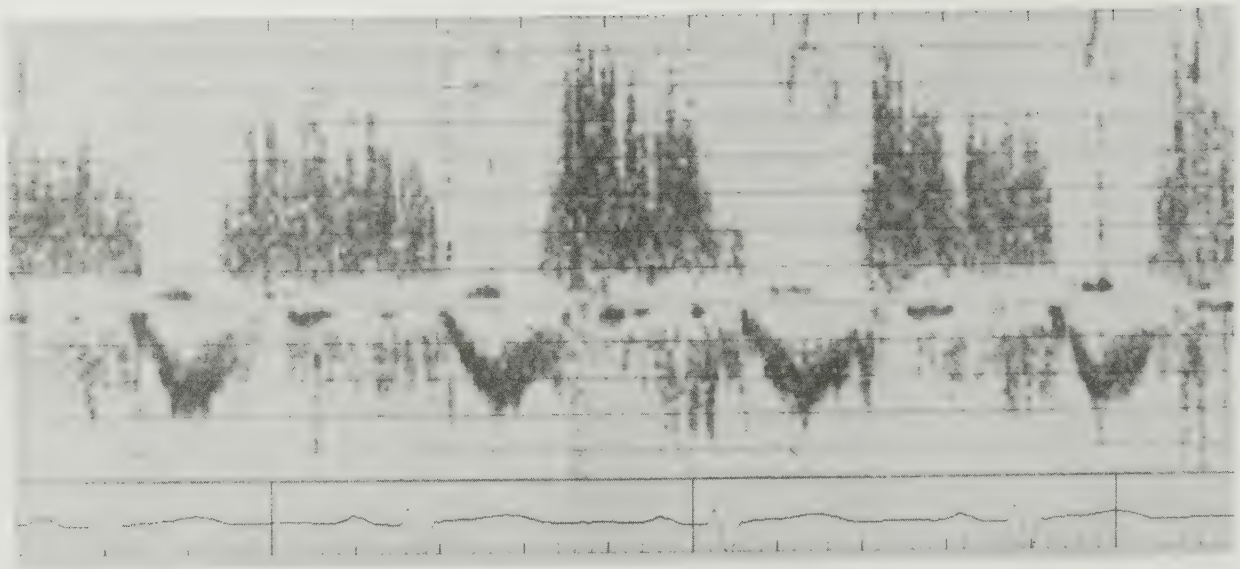

Fig. 47–7. Patent ductus arteriosus. A pulsed Doppler sample volume has been placed in the main pulmonary artery just distal to the pulmonary valve. A normal pattern of systolic flow away from the transducer is noted. In addition, there is diastolic signal toward the transducer, produced by blood that has entered the pulmonary artery through the patent ductus. Flow in the ductus is usually continuous throughout the cardiac cycle.

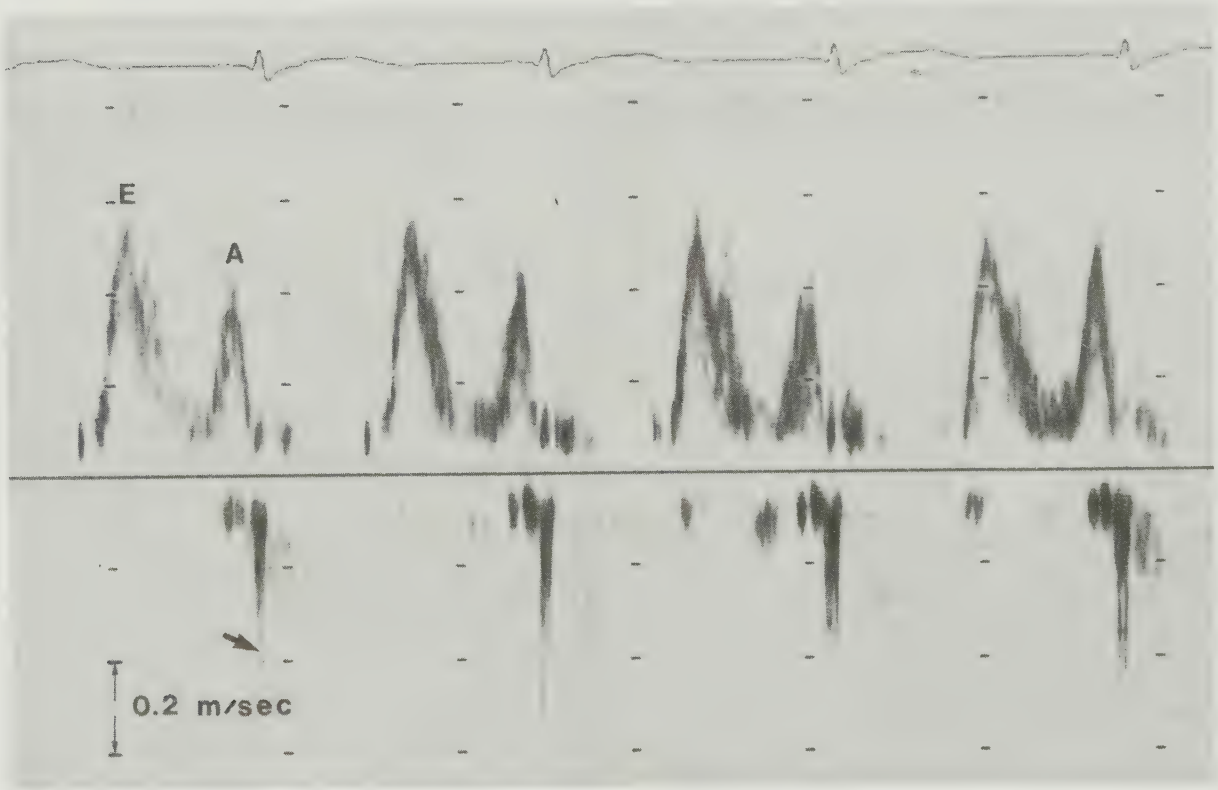

Fig. 47–8. Normal mitral inflow. Flow across the mitral and tricuspid valves is similar, characterized by a prominent early diastolic filling phase (E). Later in diastole a second filling phase (A) follows atrial systole. The onset of ventricular systole is marked by a Doppler signal produced by closure of the mitral valve (arrow).

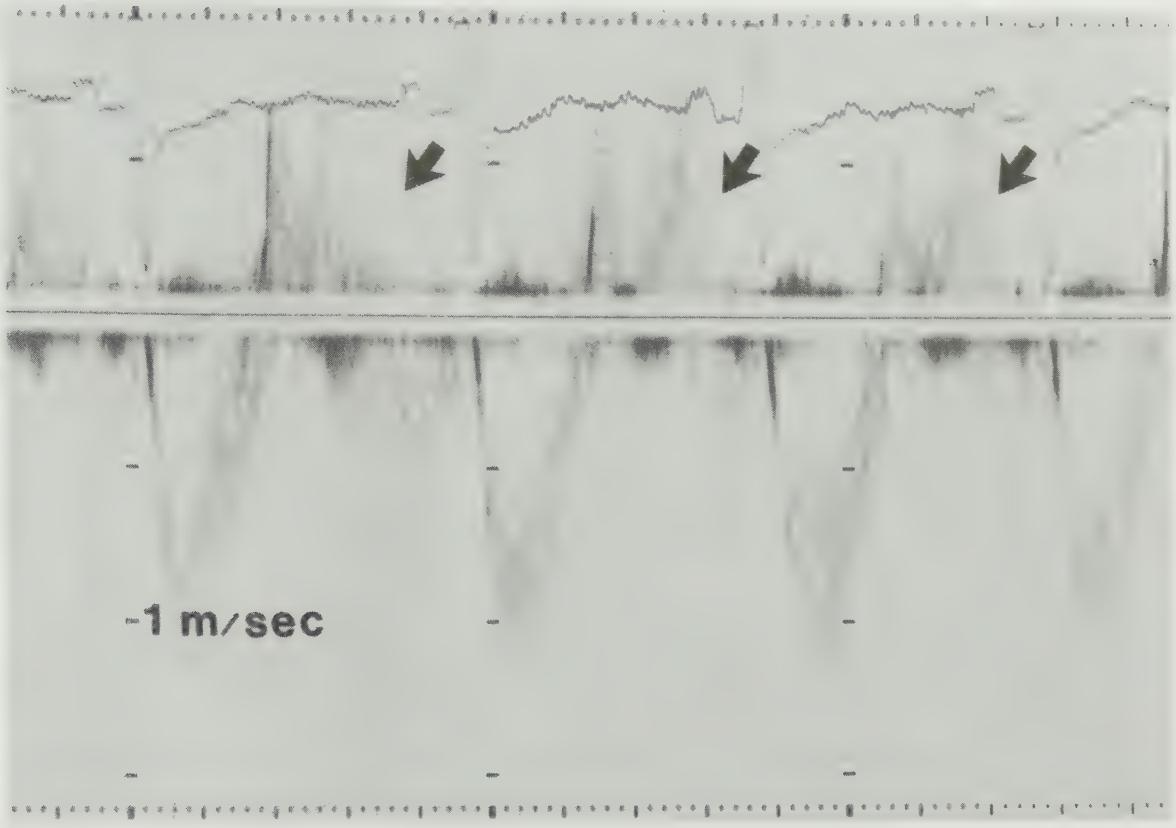

Fig. 47–9. Aortic regurgitation. A Doppler sample volume is placed in the left ventricular outflow tract immediately beneath the aortic valve leaflelts. Normal ventricular outflow pattern is present during systole. However, a signal of disturbed flow is present throughout diastole. Ordinarily, there is no diastolic flow in the subaortic region; therefore, this represents signal from an aortic regurgitation jet. The appearance of bidirectional diastolic flow is created by a circular movement of red blood cells in eddies surrounding the regurgitation jet.

Doppler sampling of flow in the left ventricular outflow tract is best performed from the apical window. The subaortic region also can be examined from the parasternal location.

Aorta

Flow in the aorta occurs almost exclusively in systole, and normal velocities range from 60 to 150 cm/sec. The brief amount of diastolic flow that enters the coronary arteries is generally undetectable during the normal Doppler examination (Fig. 47–10). Flow reversal in the aorta indicates significant runoff either due to aortic regurgitation[93] or to systemic runoff into a low pressure system through a patent ductus arteriosus aortopulmonary window or atrioventricular malformation.[94] Increased velocities in the aorta may reflect increased cardiac output such as occurs with anemia. Higher aortic velocities may be associated with Still's murmurs in normal children.[95,96]

Disturbances due to localized stenosis can occur in the ascending aorta due to aortic valve abnormalities[1,2,75] or supravalve stenosis. In the proximal descending aorta, the pattern found in coarctation of the aorta is pathognomonic (Fig. 47–11) when obstruction is present. The Doppler pattern consists of a continuation of forward flow throughout diastole. In addition, there is an acceleration of blood through the stenotic area and a high-velocity jet detectable at the point of obstruction.

Although flow in the proximal ascending aorta can be examined from the apical window, flow in the remainder of the aortic arch is best sampled from the suprasternal notch, or the high right parasternal location.

QUANTITATIVE DOPPLER METHODS

Measurement of Flow

The relationship between mean velocity, cross-sectional area, and volume of flow is discussed in Chapter 34. Based on that relationship, it is possible to estimate cardiac flow if one can measure the mean velocity and cross-sectional area at a given point. This provides the Doppler echocardiographer with a powerful quantitative tool, but certain conditions must be met for the Doppler estimates of flow to reflect true flow volumes: 1) flow must be laminar, and 2) the spatial velocity profile across the orifice must be relatively flat.[97–101] These criteria are necessary because the Doppler echocardiographer uses data from a single sampling point to represent mean velocities for the entire area of flow. Other assumptions include the fact that the angle of incidence between the ultrasound beam and the direction of flow must be known or nearly zero degrees. Also, the flow area is assumed to be constant during the period of flow (except when using the modified mitral flow method).[102]

Flow is the product of cross-sectional area and mean velocity.

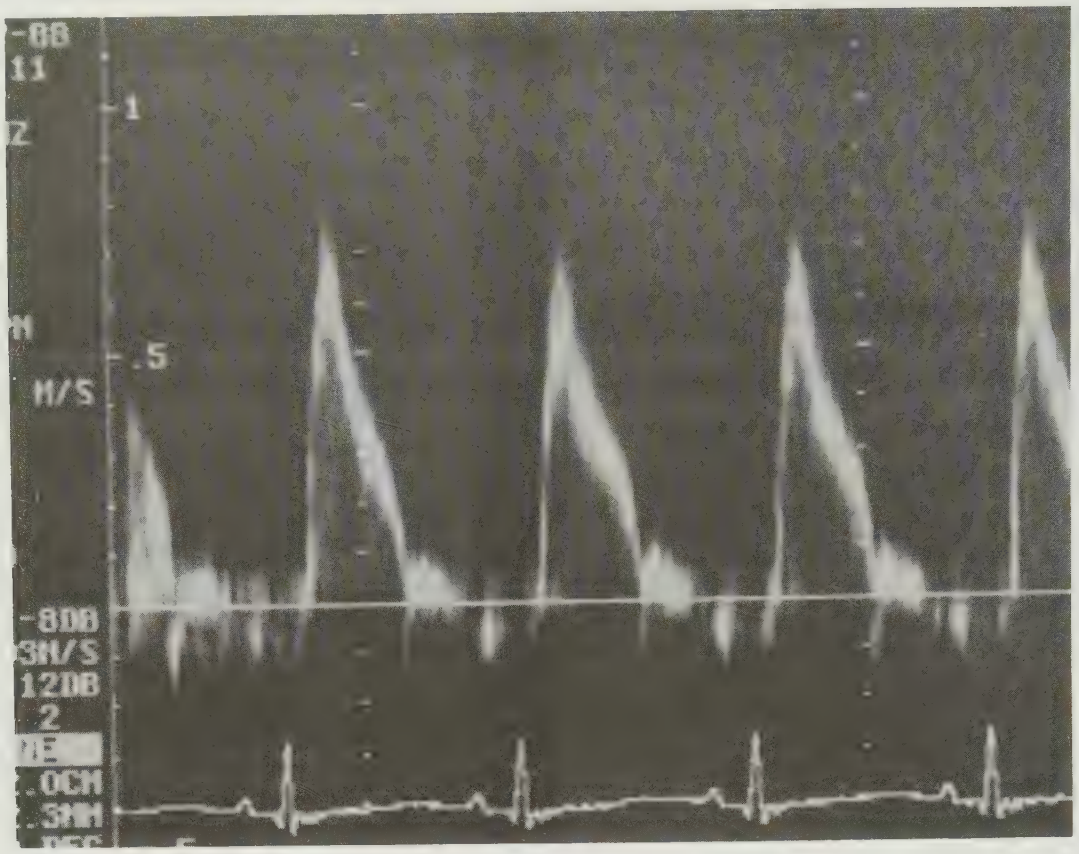

Fig. 47–10. Normal aortic flow. The Doppler sample volume is placed in the ascending aorta from the suprasternal notch. The flow occurs during systole toward the transducer (upward). A narrow range of velocities is present that produces a discrete spectral envelope. Aortic acceleration is relatively rapid with peak velocity occurring early in the ejection phase. As the flow decelerates, red cells move at different rates creating a broader deceleration envelope.

Cross-sectional area is generally obtained from the two-dimensional or M-mode echocardiogram as discussed below. Mean velocity can be obtained either for a single beat (time velocity integral) over a complete cardiac cycle, or over an arbitrary period of time. If the time velocity integral is used, then the formula for calculation of flow is:

$$\text{Flow} = \text{cross-sectional area} \times \text{TVI} \times \text{heart rate}$$

If mean velocity is measured for the complete cardiac cycle or over a specific period of time, then heart rate is not taken into account, and flow is simply the product of cross-sectional area and mean velocity. The Doppler signal used to calculate mean velocity can be from pulsed or continuous wave interrogation. When a pulsed output is obtained, the mean velocity is calculated by tracing the darkest part of the spectral display (modal velocity). When a continuous wave output is used, the tracing is usually made around the edges of the spectral envelope (maximal velocity). These methods may produce slightly different results. Whichever method is used to obtain mean velocity, at least three to five complete cardiac cycles should be measured to reduce the potential error induced by beat-to-beat variation.[103,104] When performing serial studies in the same patient, similar methods should be used from one examination to the next.

Aortic Flow

The aortic valve is the location chosen most frequently for measurement of cardiac output. There are several ways to measure aortic area (Fig. 47–12), including measurement at the insertion of the aortic valve leaflets or in the aorta above the sinuses of Valsalva from the 2DE.[100] It is also possible to use the aortic valve leaflet separation diameter as demonstrated on an M-mode echo as an estimate of aortic diameter.[105,106] The first method—namely, measurement at the insertion of the aortic leaflets—is the most reproducible method,[107–109] although it tends to underestimate true flow area slightly.[110,111] Each of these methods assumes a circular aortic shape and each is subject to large discrepancies unless extreme care is taken in the measurement process.[99,108]

Doppler recording of velocity can be performed from the suprasternal notch or the apex. Because the highest velocities occur at the aortic valve, continuous wave Doppler can be used with the assumption that the maximal velocities occur at the annulus. If pulsed Doppler is used, the sample volume is placed as close as possible to the aortic leaflets. It is desirable to have valve clicks present on the Doppler tracing for confirmation of sample volume placement. Mean velocity is obtained by measuring the area under the Doppler tracing (Fig. 47–13) and cardiac output is determined using the following formula:

$$\text{Aortic flow} = \text{mean velocity} \cdot \left(\frac{D}{2}\right)^2 \cdot \pi$$

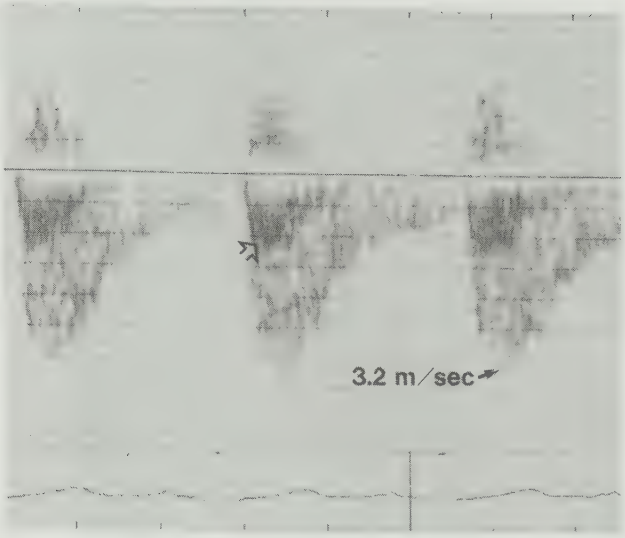

Fig. 47–11. Coarctation of the aorta. Continuous wave Doppler from the suprasternal notch directed toward the descending aorta. This tracing demonstrates Doppler signal from two populations of cells, one has a higher velocity (3.2 m/sec) with a persistence of flow into and through diastole. This pattern suggests obstruction at the site of coarctation. A second population of velocities (open arrow) can be demonstrated within the Doppler tracing.

where D is the aortic diameter. Alternatively, if the time velocity integral is used, the formula becomes:

$$\text{Aortic flow} = \text{TVI} \cdot \left(\frac{D}{2}\right)^2 \cdot \pi \cdot \text{HR}$$

Pulmonary Flow

The principles of Doppler flow measurement at the pulmonary valve are identical to those used for the aortic valve. Pulmonary artery diameter is measured from a 2DE. Unfortunately, the pulmonary artery annulus is frequently displayed in such a way that measurement is difficult without errors caused by poor lateral resolution. Pulmonary flow is best sampled using pulsed Doppler from the parasternal or subcostal positions, although a variety of locations should be used to identify the highest recordable pulmonary velocities.[112] The sample volume is moved to the pulmonary annulus as identified by valve clicks on the Doppler tracing. Optimal azimuthal angulation is obtained by listening to the Doppler audio output and manipulating the transducer to maximize the systolic velocities.

Mitral Flow

Measurement of flow across the mitral or tricuspid valve presents more potential for error. This is due to several factors including the fact that the mitral valve annulus is an elliptical structure that does not occupy a single Euclidean plane. In addition, the area of flow through the tips of the mitral leaflets changes throughout diastole as the leaflets first move apart, then re-appose and move apart again. Two methods are used for calculating mitral flow using Doppler echocardiography. The first measures flow at the mitral annulus. Doppler sampling is performed with a pulsed sample volume placed at the annulus using 2-D guidance. Mitral area is calculated either from a diameter obtained from the apical view (the orifice is assumed to be circular) or by tracing the area of the mitral annulus on the two-dimensional short axis image. Although both methods have been shown to correlate with other methods of measuring flow, there is considerable inaccuracy produced by the difficulties in measurement of the true mitral annulus area.[107,113]

An alternative method for estimation of mitral flow entails placement of a pulsed Doppler sample volume in the funnel of the mitral valve where the velocities are highest. The area at this point is calculated by measuring the leaflet separation area on an M-mode echocardiogram and normalizing for maximal mitral valve area. This method has also been shown to correlate with other methods,[102,114,115] but it is tedious and relies on several assumptions regarding the size and shape of the mitral orifice.

Tricuspid Flow

The most reasonable way to measure flow across the tricuspid valve is to sample at the annulus from the apex using pulsed Doppler. The tricuspid area is calculated by using a tricuspid diameter obtained from two-dimensional echocardiogram and assuming a circular shape.[116,117]

CLINICAL VALIDATION OF DOPPLER MEASUREMENT OF CARDIAC FLOW

There are a large number of studies validating the use of Doppler estimation of stroke volume in cardiac output in animals and adult patients.[118] There are fewer studies validating the use of this technique in infants and children. Estimates in the normal fetus,[119–121] preterm, and term newborn infants,[122,123] have been published. However, those studies did not include simultaneous invasive estimates of cardiac output, and the methodology for area measurement is different in each of the studies. Therefore, no reliable standards exist for Doppler cardiac output measurement in the fetus or infant. In fact, due to the small size of the valve orifices, the percent potential error due to a measurement inconsistency is considerably greater in the fetus or newborn than in the older child or adult.[119]

Studies have been performed in older children comparing simultaneous thermodilution or Fick estimates of cardiac output to Doppler measurements of output.[105,109,124–126] This research employs a variety of methods of both Doppler interrogation and aortic area measurement. Several studies have addressed the effect of different sites and methods of area measurement,[105,109,111] but there is no universal agreement on the ideal method for Doppler estimation of aortic flow.

Serial measurements of cardiac output in the same patient would alleviate the potential errors induced by aortic valve measurement if one assumes that the aortic diameter remains relatively constant. The value of serial measurements of aortic flow has been demonstrated during exercise[127] and during administration of pharmacologic agents.[109] In serial studies, one can expect changes of more than 10% in actual cardiac output to be accurately reflected in the Doppler measurements.[109,128,129]

Measurement of Shunt Flows

There has been a considerable interest in the development of noninvasive methods for measuring the volume of left-to-right

Fig. 47–12. Measurement of aortic area. A two-dimensional echocardiogram in the parasternal long axis view is shown. Three possible sites for measurement of the arotic cross-sectional area are demonstrated: 1) at the level of the aortic valve (AV), 2) at the aortic root at the level of the sinus of Valsalva (AR), and 3) in the ascending aorta above the sinus of Valsalva (AA). LA = left atrium, LV = left ventricle.

shunt in pediatric patients with congenital cardiac defects. In fact, in the pediatric population this may be more useful than the measurement of absolute cardiac output or stroke volume. The estimation of left-to-right shunt entails volumetric measurement at two intracardiac sites. For example, the ratio of pulmonary to systemic flow in patients with atrial septal defects can be estimated by comparing the flow measured at the pulmonary valve compared to that measured at the aortic valve. Alternatively, the tricuspid valve flow could be used for pulmonary flow estimation; likewise, the mitral valve flows could be used as an estimate of systemic flow volume. For the patient with patent ductus arteriosus, systemic flow is measured at the tricuspid or pulmonary valve and pulmonary flow is obtained at the aortic valve. The magnitude of the ductal shunt is calculated by subtracting the flow measured at the aortic valve from that measured at the pulmonary valve.

Doppler estimates of pulmonary to systemic flow ratios correlate roughly with other methods of shunt measurement.[103,130–132] However, such estimates are subject to wide variability primarily due to difficulties in accurate measurement of area. They can be used by the clinician as a semiquantitative estimate of magnitude of left-to-right shunt.

A similar approach has been used to measure regurgitant fractions or regurgitant volumes in patients with aortic or mitral regurgitation.[68,69,113–136] These calculations also require measurement of flow at at least two intracardiac sites and then the calculation of regurgitant volume by subtracting flow at one site from flow at another site. For example, aortic regurgitant volume is the difference between forward flow at the aortic valve and forward flow at the mitral valve. As with other Doppler flow estimates, these calculations require close attention to technical detail. Also, any inherent inaccuracies in the method are exaggerated by the fact that two flow estimates are being performed.

Estimation of Pressure Gradients

The theoretical basis for the use of Doppler velocities in the estimation of pressure gradients is discussed in Chapter 34. Several simplifications are made to the Bernoulli equation, and it is used clinically[137]:

$$\text{Pressure gradient} = 4(V_{max})^2$$

This equation can be applied to any pressure drop across a discrete obstruction and is useful in a variety of clinical situations. However, long segment obstructions' proximal velocities can be significant, causing an underestimation of the actual pressure gradient,[138] or relaminarization of flow can occur with loss of distal velocity and result in an overestimation of the pressure gradient using Doppler.[130] Pressure gradients across extremely small orifices can also be underestimated due to an inadequate jet formation. Finally, the shape of the orifice also has an effect on the jet that is produced and may affect the accuracy of the pressure gradient estimation.[138]

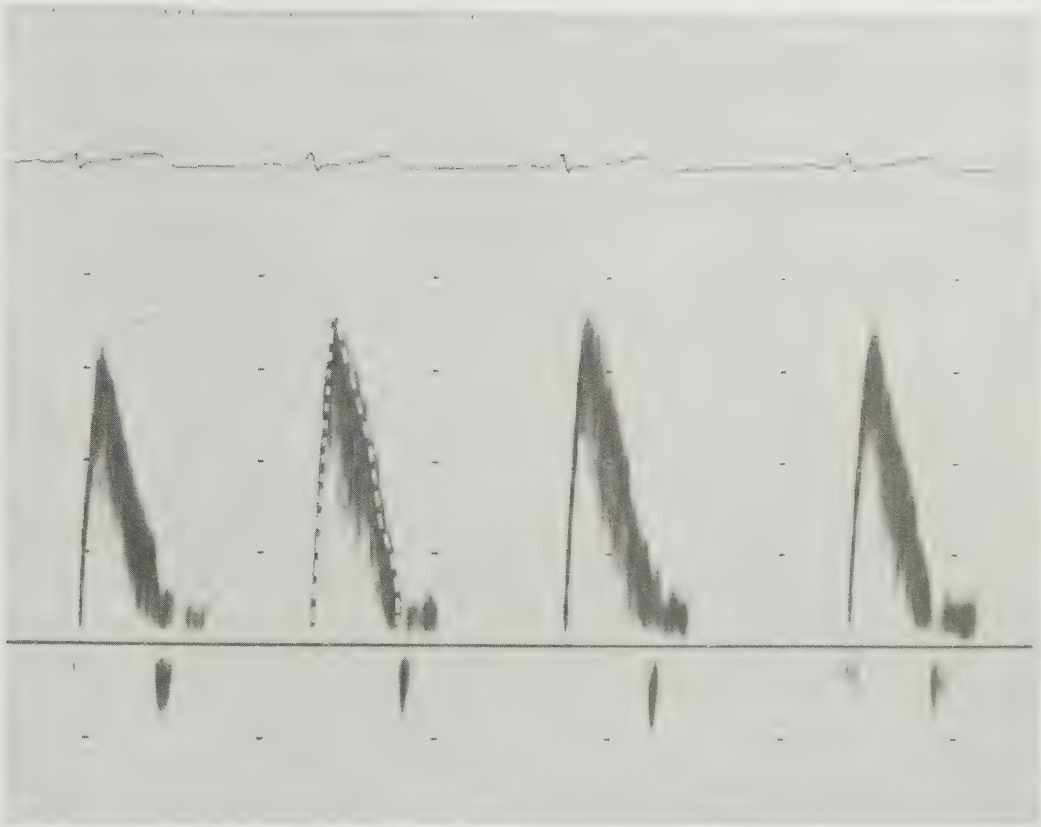

Fig. 47–13. Measurement of mean aortic velocity. A typical Doppler tracing from the ascending aorta is shown. There is a relatively narrow range of Doppler velocities that produces a discrete envelope. There is a slight increase in the range of velocities during deceleration. The method for measuring mean velocity is demonstrated. Modal Doppler velocities are traced (dotted white line) using a digitizer. Cardiac output is the product of cross-sectional area, mean velocity, and heart rate.

Clinical Use of Doppler Estimation of Pressure Gradients

Doppler echocardiography has been used to estimate the pressure gradient produced by stenosis in a variety of lesions. Good correlations between catheter measured gradients and Doppler estimated gradients have been shown for pulmonary stenosis,[36,140–149] aortic stenosis,[144,146,150–159] and mitral valve stenosis.[152,160–165] In addition, Doppler estimates correlate well with the gradients measured across subaortic obstructions,[80,81,151,166] ventricular septal defects,[167–170] pulmonary artery bands,[144,145,171,172] prosthetic valves,[173–175] surgically created shunts,[176] patent ductus arteriosus,[177,178] and coarctation of the aorta.[179,180] Doppler velocities also have been shown to correlate with severity of pulmonary venous obstruction[55] and obstruction due to a restrictive atrial septal defect.[55,181] The peak velocity of the tricuspid regurgitation jet has been used to estimate right ventricular pressure in a variety of situations.[182–186]

Estimation of pressure gradients using Doppler peak velocity allows the clinician to estimate the severity of stenotic lesions noninvasively. In addition, pressure gradient estimations and peak velocity can be used to estimate intracardiac pressure in a variety of situations. In the absence of aortic valve disease, the left ventricular systolic pressure is estimated by measuring brachial artery pressure with a sphygmomanometer. If aortic stenosis is present, peak left ventricular systolic pressure is estimated by calculating the peak or mean pressure gradients from the Doppler output of the aortic stenosis jet. When peak jet velocity is used, the peak instantaneous gradient is obtained. Peak instantaneous gradient is not identical to catheter measured peak-to-peak gradient in aortic stenosis (Fig. 47–14).[146] Peak instantaneous gradient is greater than the peak-to-peak measurement, which varies from between 70 to 84% of the maximal gradient.[154,158,187,188] On the other hand, in pulmonary stenosis, peak instantaneous gradient occurs in mid-systole and corresponds closely with peak-to-peak gradient (Fig. 47–15).[146,149,184]

Right ventricular systolic pressure can be estimated if tricuspid regurgitation or a ventricular septal defect is present. The peak velocity of the tricuspid regurgitation jet is converted to pressure gradient using the modified Bernoulli equation. This value is then inserted into a regression equation or more simply added to a clinical estimate of right atrial pressure. For example, if a tricuspid regurgitation jet of 3.5 m/sec peak velocity is obtained, this yields an estimated pressure gradient between right ventricle and right atrium in systole of 49 mm Hg. If the clinical estimate of right atrial pressure is 6 mm Hg, then the estimated right ventricular systolic pressure is 55 mm Hg. In the absence of right ventricular outflow tract obstruction, this would allow estimation of pulmonary artery systolic pressure of 55 mm Hg also. If, on the other hand, there is obstruction to right ventricular outflow, Doppler estimation of the gradient across the stenotic area allows estimation

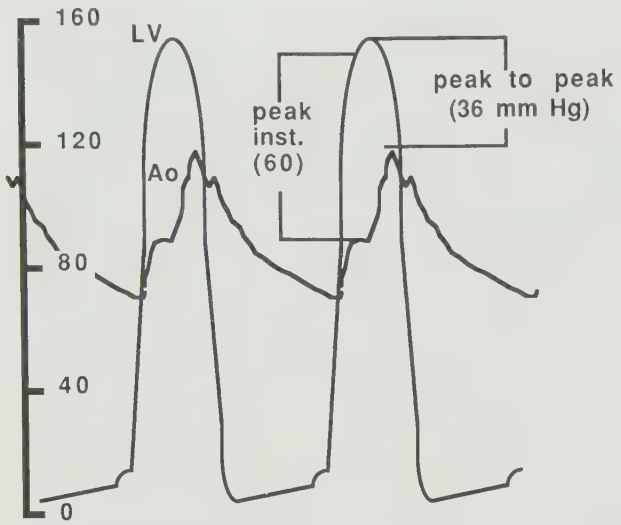

Fig. 47–14. Pressure gradients in aortic stenosis. A diagrammatic representation of aortic and left ventricular pressure tracings demonstrate the difference between peak instantaneous and peak-to-peak pressure gradients. Peak instantaneous gradient occurs early in systole. Peak-to-peak pressure gradient does not reflect simultaneous pressure readings. In aortic stenosis, peak-to-peak pressure gradient is generally 60 to 75% of peak instantaneous gradient.

of pulmonary arteries' systolic pressure. For example, if in the previous case a peak velocity across a stenotic pulmonary valve of 3 m/sec is obtained, pulmonary artery systolic pressure is estimated to be 55 mm Hg less the estimated gradient of 36 mm Hg, which equals 19 mm Hg.

The presence of a ventricular septal defect also provides an opportunity to estimate right ventricular systolic pressure. First, left ventricular systolic pressure is estimated or measured; then the peak velocity of the jet across the ventricular septal defect is obtained. Because of differences in the contraction sequence of the two ventricles, peak instantaneous gradients of 15 to 25 mm Hg may exist, even though peak systolic pressures are equal in the two ventricles. Therefore, ventricular septal defect jets less than 2.5 m/sec do not necessarily correlate with a right ventricular

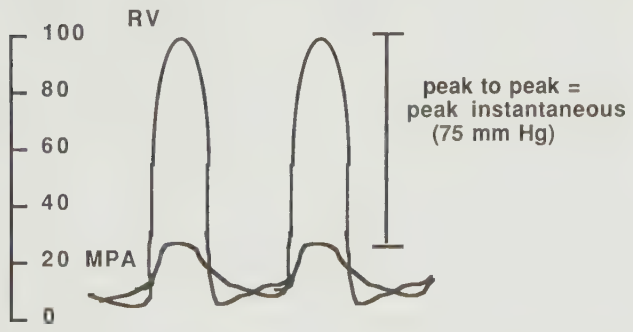

Fig. 47–15. Pressure gradients in pulmonary stenosis diagrammatic representation of pulmonary artery and right ventricular pressure tracings demonstrate that peak instantaneous and peak-to-peak pressure gradients occur in midsystole simultaneously. Therefore peak instantaneous pressure gradient is nearly identical to the peak-to-peak measurement.

systolic pressure that is less than that of the left ventricle. However, higher peak velocities allow reasonably accurate estimation of interventricular pressure differences and subsequent calculation of right ventricular systolic pressure.[169] Estimates of right ventricular pressure are particularly accurate when two independent methods are used in its estimation, thereby providing confirmatory evidence.

Estimation of systolic and mean pulmonary artery pressures is possible using peak and mean gradients from Doppler tracings of flow across both patent ductus arteriosus[177,178] and surgically created shunts.[176] As with all Doppler velocity estimates, this requires careful attention to technique and alignment of the Doppler beam as close to the axis of flow as possible. However, even if precise pulmonary artery pressures cannot be estimated, the technique can be useful clinically. For example, if an infant with transposition of the great arteries has a patent ductus arteriosus, the presence of a 3.5 m/sec systolic jet across the patent ductus insures that pulmonary artery systolic pressure is at most 50 mm Hg less than aortic pressure. This may reassure the clinician that significant pulmonary hypertension is absent and obviate the need for cardiac catheterization.

Other methods are available that use Doppler information to calculate pulmonary artery pressures. These include: 1) estimation of the mean and diastolic pulmonary artery pressure from pulmonary regurgitation;[189] 2) estimation of pulmonary artery pressure using Doppler derived systolic time intervals;[190–192] and 3) use of the ratio of pulmonary artery acceleration time to ejection time.[191,193–195] Although the statistical correlation of these methods with catheter measured pressures has been good, the wide variability and scatter makes individual estimates of pressure somewhat unreliable.

Theoretically, left ventricular diastolic pressure can be estimated using the peak velocity of the aortic regurgitation jet.[196] This end-diastolic gradient is subtracted from the aortic diastolic pressure to yield left atrial pressure. Similarly, in the presence of mitral regurgitation the peak velocity of the regurgitant jet is used to estimate a systolic pressure gradient between left ventricle and left atrium.[196] The difference between the cuff systolic blood pressure and the pressure gradient theoretically yields the left atrial systolic pressure. Unfortunately, the magnitude of left ventricular end-diastolic or left atrial pressure is frequently small. Therefore, slight errors in either cuff measurement of blood pressure or Doppler measurement of peak velocity will result in sizeable errors in estimation.

The following guidelines should be used in any quantitative estimate of peak velocity. First, perform a careful two-dimensional and pulsed Doppler study to determine which structural abnormalities and flow disturbances are present. This is particularly important when using continuous wave Doppler due to the inherent range ambiguity of the technique. Second, when possible, identify the jet of interest using pulsed Doppler or color Doppler first and then switch the Doppler unit to high-pulse repetition frequency Doppler or continuous wave Doppler for an initial estimate of the jet velocity. Third, use the audio signal to obtain the highest possible Doppler velocity. The transducer is moved so that the angle between the jet and the Doppler beam is as close to zero as possible. In general, correction for an assumed angle of incidence is not advisable. Fourth, interrogate the jet from as many echocardiographic windows as possible. For example, the jet of pulmonary

stenosis can be interrogated from the left parastenal, subcostal, apical, and suprasternal transducer positions. The jet caused by aortic stenosis is accessible from the apex, the high right parasternal location, and the suprasternal notch. Using a variety of echocardiographic windows increases the likelihood that the examination will yield the highest possible velocities.[36,112,156] Fifth, use different transducers for the examination of the same jet. Each transducer has an unique "footprint"; some may be better than others in a particular situation. Sixth, whenever possible, obtain flow information at the time of measuring a gradient. This increases the usefulness of the gradient estimation and allows meaningful serial comparisons. Finally, remember that Doppler peak velocity estimates the peak instantaneous gradient. For some lesions, such as pulmonary valve stenosis, peak instantaneous gradient occurs in midsystole and corresponds very closely with catheter-measured peak-to-peak gradient and mean gradient.[146,187] However, for aortic stenosis, peak instantaneous gradient (and peak velocity) occurs in early systole and exceeds both peak-to-peak and mean gradient.[146,154,188,197] However, Doppler estimated mean gradient correlates extremely well with catheter measured mean gradient.[154,188]

Stenotic Valve Areas

The gradient across a stenotic valve is not the sole indicator of the severity of obstruction. The presence and magnitude of a pressure gradient depends on the flow across the valve. For example, a newborn infant with critical aortic stenosis and low cardiac output may generate a small transaortic pressure gradient that will be reflected by a low peak velocity measured by Doppler. Alternatively, an older child with only moderate aortic stenosis may generate an extremely high peak instantaneous gradient during peak exercise. Another example of the limitation of peak velocity alone as an estimate of severity of obstruction occurs with mitral stenosis. Even with severe mitral obstruction, the pressure generated in the atrium is relatively low, and peak velocity does not vary directly with severity of obstruction. Therefore, Doppler velocity information should be used in conjunction with measurement of the amount of flow across the obstruction. This can be accomplished in one of two ways. Flow can be measured at a site different from that where the obstruction is present. For example, in the case of aortic stenosis, flow could be measured across the mitral valve,[198] or the pulmonary valve if there is no intracardiac shunt. An alternative approach is to use the continuity equation, which is based on the fact that flow volume is the same immediately proximal to the obstruction as it is in the obstructive jet itself (Fig. 49–16). Therefore, since flow is the product of mean velocity and cross-sectional area:

$$\text{Flow} = \text{area(proximal)} \times \text{mean velocity(proximal)}$$

$$= \text{area of obstruction} \times \text{mean velocity (jet)}$$

Solving for the area of obstruction:

$$\text{Area of obstruction} = \frac{\text{area(proximal)} \times \text{mean velocity(proximal)}}{\text{mean velocity (jet)}}$$

For aortic stenosis, the proximal area is measured using a two-dimensional echocardiogram measuring just proximal to the aortic valve. Proximal mean velocity is obtained using a pulsed Doppler sample volume placed in the left ventricular outflow tract. Care must be taken not to advance the sample volume too close to the aortic valve or the area of pre-jet acceleration will be entered. Mean jet velocity is obtained by using continuous wave Doppler and obtaining the maximal velocities in the jet itself. The mean velocity is obtained by obtaining the area under the jet velocity curve. Multiple reports have validated the use of the continuity equation in adults with aortic valve disease.[188,199–205]

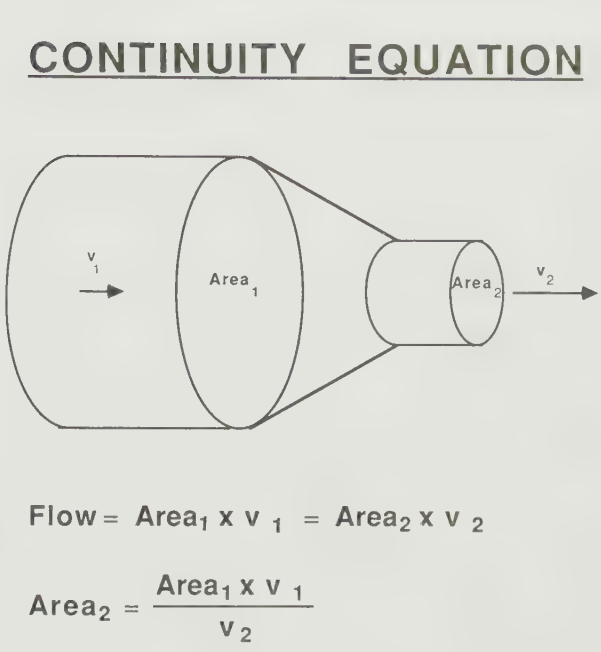

Fig. 47–16. The continuity equation for estimation of valve area.

Mitral Valve Area

Valve area in mitral stenosis can be calculated from peak or mean mitral velocity jets using a variety of formulas. However, the most successful method that is relatively independent of transvalvular flow uses the pressure half-time concept[152,162–165,206–208]:

$$\text{Mitral valve area (cm}^2\text{)} = \frac{220}{\text{pressure half-time (msec)}}$$

For use with Doppler measurements, the mitral inflow jet is obtained, and velocity measurements are converted to pressure estimates for pressure half-time measurement. This is done by dividing the peak velocity by 1.4. The point at which velocity reaches that magnitude is marked and the time from peak velocity to that point is measured. This time corresponds to the pressure half-time.

Diastolic Function

Ventricular inflow produces a plot of blood velocity versus time. These inflow velocities reflect the balance between pressure and volume during diastole and may indicate ventricular compliance. The normal ventricular inflow pattern is characterized by an early diastolic filling phase and a late filling phase following atrial contraction. Ventricular diastolic function is responsible to some extent for the relative peak velocities of these two phases as well as

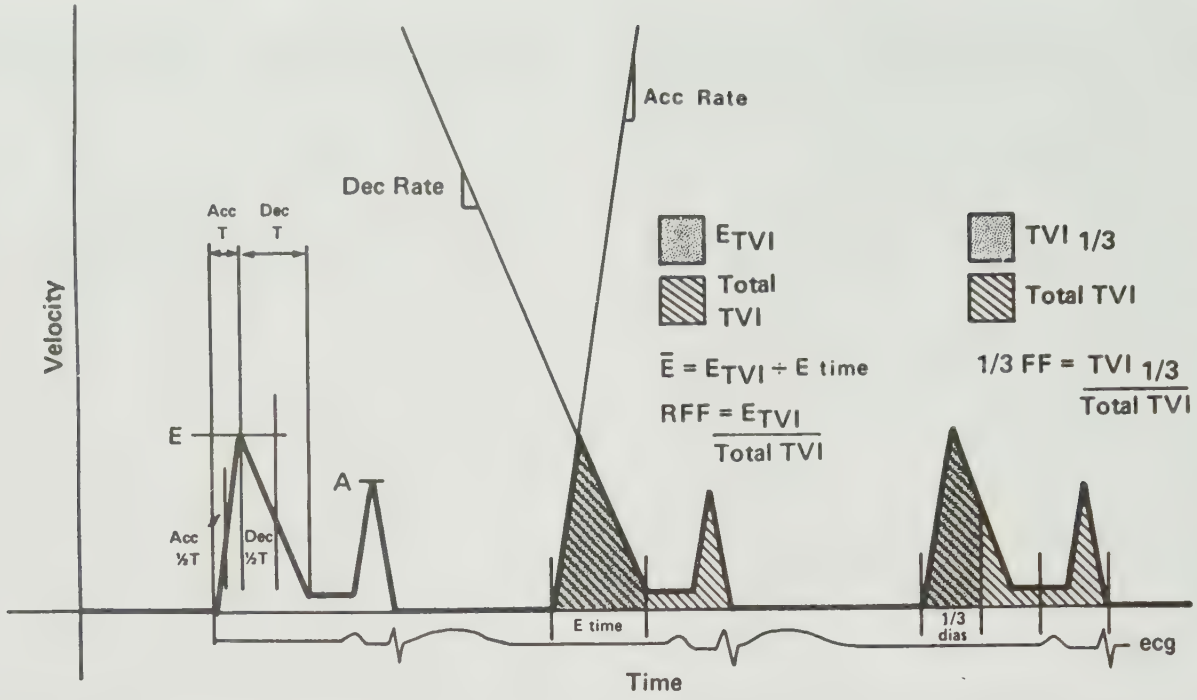

Fig. 47–17. Previous published Doppler parameters of diastolic function. ACC = acceleration; DEC = deceleration; FF = filling fraction; RFF = rapid filling fraction; T = time; TVI = time velocity integral. (Reproduced with permission from Snider, A.R.: Prediction of intracardiac pressures and assessment of ventricular function with Doppler echocardiography. Echocardiography, *3*:36, 1986).

the proportion of filling that occurs during each phase and the rate at which ventricular filling occurs.

Some studies have demonstrated good correlation between Doppler estimates of peak filling rates and similar determinations made using angiographic[209] or radionuclide methods.[210,211] Other studies have shown differences between different methods.[212] In addition to filling rates, a variety of Doppler indices of diastolic function have been used.[213,214] They include a simple ratio of peak early diastolic velocity (E) to peak late diastolic velocity (A), early diastolic acceleration and deceleration times, half-times, and filling rates. In addition, using the integral under the Doppler curve as an estimate for filling volume, a number of filling fractions have been measured for use as indicators of ventricular compliance.

As compliance decreases and the ventricle becomes stiffer, early diastolic filling velocities fall. As stroke volume falls, left atrial pressure rises, which in turn leads to increasing filling velocities; but filling occurs over a longer period of time. Therefore, reduced ventricular compliance is manifest in the ventricular inflow Doppler tracing as a reduction in peak early diastolic filling velocity and the prolongation of the early filling phase. Because of the late diastolic redistribution of inflow that occurs as a compensatory mechanism, early filling fraction is reduced and A:E ration is increased (Fig. 47–17).[213]

Left ventricular diastolic filling has been shown to change with age. In fact, the use of Doppler echocardiography has made possible examination of ventricular inflow patterns in the fetus. The normal fetal pattern includes reversed E:A ratio with higher late diastolic rather than early diastolic peak filling velocities. This is true for both the mitral and tricuspid valves.[215] As the fetus nears term, early filling velocities increase, lowering the A:E ratio.[216] After birth, the A:E ratio normalizes, and in adults peak filling rates tend to decrease with advancing age.[217]

Studies in adult patients have demonstrated Doppler inflow abnormalities in dilated cardiomyopathy,[218] restrictive ventricular physiology,[10] hypertrophic cardiomyopathy,[219,220] coronary artery disease,[221,222] primary pulmonary hypertension,[223] and systemic hypertension.[224]

Thus far, diastolic ventricular function has been characterized in normal children as well as children with systemic hypertension and children with hypertrophic cardiomyopathy. Whether these techniques will be applicable to children with congenital heart disease awaits further study.

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CHAPTER 48

Fetal Echocardiography

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The ability to observe the human fetus in utero with transabdominal ultrasonography has revolutionized obstetric diagnosis and treatment of fetal disease. Likewise, the use of echocardiography in the human fetus has paralleled the development of echocardiographic technology and has permitted early diagnosis of structural and functional abnormalities of fetal circulation. Early application of M-mode cardiac ultrasound to cardiac imaging in the human fetus was first reported by Garrett and Robinson.[1] Egeblad and associates[2] recognized the atrioventricular septum in the fetus using M-mode echocardiography, and M-mode echocardiographic parameters of ventricular size and function have since been developed.[3] The use of two-dimensional echocardiography in the diagnosis of structural congenital heart disease was pioneered by Allan and associates[4] and Kleinman and associates.[5] The accurate diagnosis and effective treatment of fetal arrhythmias are now possible as a result of M-mode and pulsed Doppler echocardiography. Thus the full range of fetal cardiac disease can be investigated noninvasively, allowing appropriate and timely treatment of the affected fetus.

FETAL CIRCULATION

Accurate diagnosis of heart disease in the fetus requires an appreciation for the basic differences between the circulation of the fetus and the circulation of the neonate adapted to extrauterine life. The circulation of the fetus is described in Chapter 15 of this text. A brief description of the major features of fetal circulation follows.

The placenta is the organ of gas exchange, nutrient supply, and waste elimination in the fetus and therefore must receive a major proportion of fetal cardiac output. In addition, the fetal lungs and bowel are active only in a metabolic sense and do not contribute directly to gas exchange and nutrient supply. Three cardiovascular shunts exist in the fetus to accomplish the distribution of oxygen and nutrients to the fetus and carbon dioxide and other products of metabolism to the placenta. These are the ductus arteriosus, ductus venosus, and foramen ovale cordis. Because of the presence of these cardiovascular shunts, the fetal circulation functions in parallel rather than in series as in the adult. Fetal cardiac output, therefore, may be described only in terms of combined ventricular output.

The venous return to the fetal heart by the inferior vena cava is directed primarily to the foramen ovale and left atrium by the eustachian valve, although a small percentage of inferior vena caval return is directed to the tricuspid valve.[6] Inferior vena caval return is primarily composed of umbilical venous flow directed to the inferior vena cava by the ductus venosus with the addition of portal and hepatic venous flow. Therefore the oxygen-rich umbilical venous return ultimately enters the left ventricle and is distributed to the fetal head and upper body. The output of the left ventricle represents approximately 30% of combined ventricular output in the fetal lamb[7] and has an oxygen saturation of approximately 65%. Total umbilical venous flow therefore represents placental blood flow returning to the fetus. The superior vena caval return, representing venous flow from the fetal head and upper body, is directed primarily through the tricuspid valve to the right ventricle. The superior vena caval return and a portion of inferior vena caval return are ejected from the right ventricle, where the majority, approximately 60% of combined ventricular output,[8]

enters the ductus arteriosus and supplies the descending aorta. Approximately 10% of the ascending aortic flow in the fetal lamb enters the descending aorta by way of the aortic isthmus. Umbilical arterial flow in the paired umbilical arteries arising from the descending aorta represents approximately 40 to 50%[8] of combined ventricular output and is the arterial supply to the placenta on the fetal side.

The proportion of blood flow to fetal organs varies with gestational age, metabolic activity of the organ, organ growth, and species.[8] The proportion of blood flow to the fetal head and lungs increases with increasing gestational age, whereas the proportion of blood flow to the fetal heart remains approximately the same. In the human fetus, the proportion of combined ventricular output ejected by the left ventricle is greater than that in the fetal lamb, probably as a result of the greater mass of cerebral tissue in the human fetus.[9–11] Nonetheless, in the human as in the lamb, the right ventricle supplies the greatest contribution to descending aortic flow and consequently to umbilical arterial flow. Therefore heart failure in the fetus is often initially accompanied by right ventricular enlargement and ultimately by signs of right ventricular failure such as ascites, edema, and pleural and pericardial effusions.[12,13]

INDICATIONS FOR FETAL ECHOCARDIOGRAPHY

Among the many indications for fetal echocardiography,[14–17] a number of maternal factors may predispose the fetus to structural or functional abnormalities of the heart. Congenital heart disease in the mother, father, or siblings increases the risk of congenital heart disease in the fetus. Maternal exposure to known cardiac teratogens such as the rubella virus or lithium or to other potentially teratogenic environmental agents necessitates careful examination of the fetal heart. Maternal disease may produce abnormalities of cardiac structure, function, or heart rate in the fetus. Reduced cardiac function and septal hypertrophy may be recognized in infants of poorly controlled diabetic mothers. Congenital AV block is often associated with maternal autoimmune disease such as systemic lupus erythematosus. Reduced placental blood flow and elevated placental resistance may be recognized in toxemic pregnancies associated with intrauterine growth retardation.

Among the fetal indications for cardiac ultrasound, the most common cause for referral is the recognition of fetal abnormalities detected on routine obstetric ultrasonic examination. Abnormal fetal cardiac structure may be demonstrated in the course of obstetric examination of the fetal thorax. Fetal polyhydramnios may be associated with abnormalities of cardiac structure and function in addition to other congenital defects. The development of nonimmune fetal hydrops should lead to fetal echocardiographic examination to exclude structural heart disease or fetal arrhythmia. Cardiac failure in the fetus is manifest on routine obstetric ultrasound as cardiac enlargement in association with nonimmune hydrops.[12,13] Serial assessment of cardiac function may be useful in fetuses with hemolytic disease and associated hydrops. Abnormalities of fetal heart rate and rhythm are being recognized with increasing frequency because of widespread use of antepartum fetal heart rate monitoring; these abnormalities often lead to fetal echocardiographic examination. Accurate assessment of fetal arrhythmias then allows effective treatment to be instituted. The detection by amniocentesis of chromosomal abnormalities that are known to predispose to cardiac disease, such as trisomy 21, should lead to referral for fetal echocardiography.

FETAL CARDIAC ULTRASOUND METHODOLOGY

In the following section we will explore the application of echocardiography to examination of the fetal cardiovascular system. The methodological approach to the fetal echocardiographic examination will be described, emphasizing the application of fetal echocardiography to the diagnosis of structural heart disease, diagnosis of arrhythmia, assessment of fetal heart function, and assessment of placental blood flow and resistance.

Instrumentation

There is no system that is ideally suited to every application of echocardiography in the fetus. Conventional linear array obstetric scanning instruments offer the advantage of improved depth of penetration, improved image resolution, and a rectangular image, allowing full visualization of the fetus. However, the relatively large linear-array scanheads are cumbersome and do not easily rotate around an axis with the fetal heart at the center. In addition, duplex Doppler imaging has only recently become available on linear array systems and employs an independent offset Doppler crystal. The availability of combined two-dimensional and M-mode imaging, essential for obtaining accurate chamber dimensions and for the accurate diagnosis of fetal arrhythmias by M-mode echocardiography, is standard in mechanical and phased-array cardiac imaging systems.

Mechanical and phased-array sector scanning systems offer good image resolution and in-line M-mode and duplex Doppler. There are some disadvantages to mechanical and phased-array sector-scanning instruments. Unfortunately, to achieve adequate penetration, a relatively low carrier frequency in the range of 3 to 5 mHz must be used. In examining the fetal heart, the use of transducer frequencies in this range results in significantly reduced image resolution. Dynamically focused anular-array imaging systems offer improved image resolution. In any sector scanner, far-field images are inferior because of reduced line density with increasing distance from the transducer.

Pulsed and continuous-wave Doppler may be performed with linear-array, phased-array, or mechanical systems in carrier frequency ranges from 2 to 5 mHz. Lower carrier frequencies allow greater depth of penetration for Doppler examination. When continuous-wave Doppler interrogation of the fetus is absolutely necessary, linear- and phased-array systems offer the advantage of two-dimensional guidance of the continuous-wave beam. In summary, both sector scanning and linear scanning offer advantages to the fetal echocardiographer and should be used in a complementary fashion to achieve the best possible diagnostic accuracy.

INITIAL OBSTETRIC ULTRASOUND EXAMINATION

In conjunction with fetal cardiac imaging, a complete obstetric ultrasound examination of the fetus should be performed by a qualified perinatologist. An accurate assessment of fetal gestational age using fetal biparietal diameter, abdominal circumference, or femur length should accompany fetal cardiac examination. An assessment of appropria e fetal growth is useful in identifying

either growth-retarded fetuses or fetuses that are large for gestational age. As was noted above, fetal edema, ascites, and pleural effusion may be noted by the obstetric examiner in patients with fetal hydrops secondary to congestive heart failure. An assessment of the degree of hydrops is important in evaluating therapy for congestive heart failure secondary to structural heart disease or fetal arrhythmia. It is also important to note the presence or absence of congenital defects affecting organ systems that may be associated with congenital heart disease. In addition, routine obstetric scanning of the fetus before fetal echocardiography should include an assessment of fetal cardiac structure, emphasizing recognition of a normal four-chambered heart.

CARDIAC IMAGING

After a careful obstetric examination has been performed and an accurate assessment of fetal gestational age has been obtained, the examination is directed to cardiac imaging. An adequate cardiac ultrasound to exclude serious congenital heart disease can be performed in the great majority of patients at greater than 18 weeks gestation. However, the examination may be limited by fetal mobility, particularly early in gestation, and by fetal position. As the fetus matures, ossification of the ribs and vertebral bodies adds to the difficulty of obtaining adequate images. The occiput anterior position with an anterior placenta is most troublesome because the fetal spine and the placenta lie between the echocardiographic transducer and the fetal heart. Other factors that may impair imaging include maternal obesity, advanced fetal edema, and polyhydramnios.

A traditional "view"-oriented approach to imaging of the fetal heart is difficult because of lack of control of fetal position and the resulting unconventional orientation of cardiac images. A segmental approach that emphasizes visualization of venous, atrial, ventricular, and great vessel connections is preferable to a "view"-oriented approach. Nonetheless, an attempt is made to obtain images in at least three conventional imaging planes: the short-axis, four-chamber, and long-axis planes. Images that are comparable to the suprasternal notch views obtained postnatally can also be obtained in many fetuses.

The examination begins by establishing fetal position in the maternal abdomen. In cross section of the maternal abdomen, the mother's left is displayed on the right-hand side of the video screen. In the maternal sagittal plane, the mother's head is to the right of the screen, and the symphysis pubis is to the left. In this way, maternal landmarks can be used to provide orientation of fetal position. After establishing orientation of the fetus wth respect to the mother, the fetus is scanned to determine the position of the fetal head and spine. This establishes the anterior/posterior and left/right orientation of the fetus. For instance, when the fetus is vertex with occiput anterior, the fetal spine will be anterior and the left of the fetus in cross section will be to the right of the video screen. If the fetus is vertex with occiput posterior, the left of the fetus in cross section will be to the left-hand side of the video screen. With breech presentation, these relationships are reversed. The fetus is likely to change position within the maternal abdomen, and fetal position must then be reestablished with respect to the maternal abdomen. The examiner should avoid the temptation to reverse video image orientation when fetal position changes or to obtain conventional cardiac image orientation. Doing so could lead to great confusion of right and left in the fetus, which could lead to errors in the diagnosis of cardiac or visceral situs and ventriculoarterial connection.

After establishing fetal position, the examination is directed to the fetal thorax and abdomen. Scanning from cephalad to caudad in the transverse plane establishes cardiac position in the chest and position of the descending aorta and inferior vena cava. Because the lungs are filled with fluid and the liver is large, the usual orientation of the heart is to the left and horizontal with the apex clearly directed to the left. Thus scanning in a sagittal plane parallel to the fetal spine produces short-axis images. A diagnosis of dextrocardia is made when the fetal heart is in the right chest, usually with the cardiac apex directed to the right. However, when dextrocardia is produced by displacement of the heart from the left hemithorax, as in left diaphragmatic hernia, the apex may be in the midline or directed to the left, and the herniated abdominal contents will be visible.

In assessing atrial and visceral situs, the position of the inferior vena cava and the descending aorta relative to the fetal spine are critical.[18] In atrial situs solitus, the inferior vena cava courses to the right and anterior to the fetal spine and descending aorta. The descending aorta is to the left and anterior to the fetal vertebral bodies, and the inferior vena cava is anterior to the descending aorta. The inferior vena cava and superior vena cava enter the right atrium, whereas the left atrium has no systemic venous connection. In situs inversus, this relationship is reversed; the inferior vena cava is on the left and anterior to the fetal spine and the descending aorta is on the right. In right atrial isomerism, the descending aorta and inferior vena cava are usually together on either side of the fetal spine with the inferior vena cava anterior to the descending aorta. In left atrial isomerism, the aorta is usually midline with absence of the suprarenal inferior vena cava and with azygous continuation (Fig. 48–1). The azygous vein is almost always posterior to the descending aorta but could be to either side of the fetal spine. In addition, with left atrial isomerism, there is total anomalous hepatic venous connection with the hepatic veins connecting directly to the atria. Atrial situs may also be determined by demonstrating characteristic morphology of the atrial appendages (Fig. 48–2). Visceral situs may be demonstrated by the position of the fluid-filled stomach on either the left or the right. However, the left lobe of the liver is larger in utero than in postnatal life; therefore the presence of a large left lobe of the liver does not imply situs ambiguous or inversus.

After assessing the pattern of venous connection to the heart, an assessment of atrial morphology in the normal fetus often reveals a large eustachian valve in the right atrium directing inferior vena caval return to the foramen ovale. The septum primum will be directed toward the left atrium in utero (Fig. 48–3). The existence of a secundum atrial septal defect therefore cannot be excluded in utero. However, common atrium and the characteristic morphology of the atrial component of complete or incomplete atrioventricular canal defects are usually clearly identified (Fig. 48–4). These abnormalities are best appreciated in the four-chamber plane. The morphology of the atrioventricular valves is also assessed in the four-chamber plane, as is the atrioventricular connection (Fig. 48–5). Normal valve motion can be demonstrated by both two-dimensional and M-mode echocardiography. The relative size of the tricuspid and mitral valves should be noted; they are approximately the same size in a normal fetus.

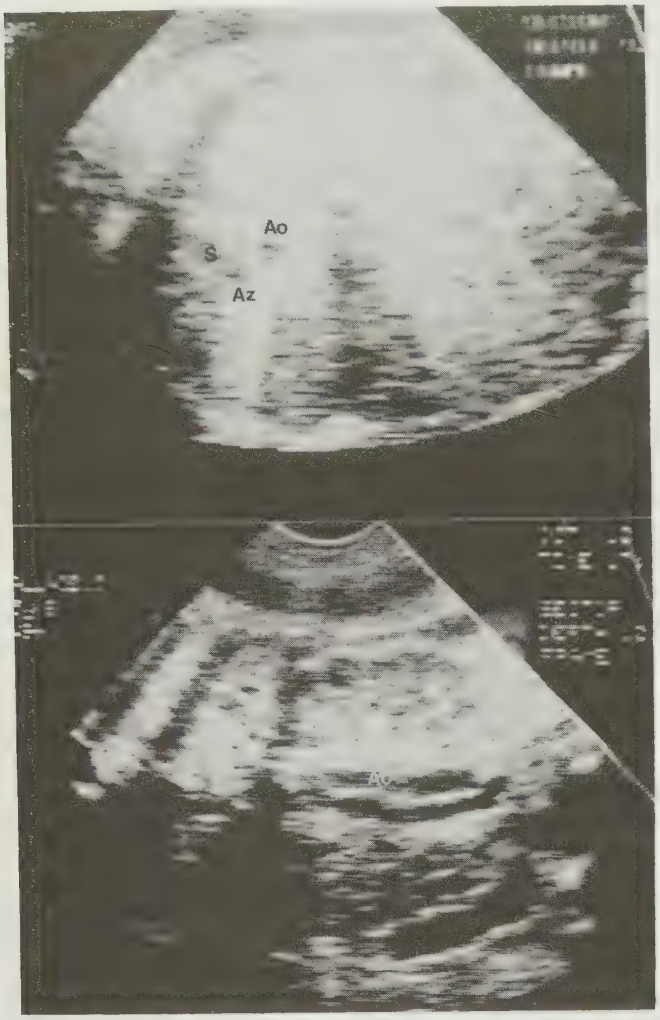

Fig. 48–1. Transverse (upper panel) and sagittal (lower panel) two-dimensional echocardiograms of the fetal abdomen demonstrating absence of the suprarenal inferior vena cava with azygous continuation. The azygous vein (Az) is posterior to the aorta (Ao). These findings are compatible with left atrial isomerism. In atrial situs solitus, the aorta is anterior to the fetal spine, and the inferior vena cava is to the right and anterior to the aorta. S = fetal spine.

Establishing atrioventricular connection requires demonstration of the characteristic morphologic features of the left and right ventricles. The tricuspid valve is located nearer the cardiac apex than the mitral valve. The inferior position of the tricuspid valve is actually a characteristic of normal right ventricular morphology, although extreme apical displacement of the tricuspid valve with gross right atrial enlargement is seen in the fetus with Ebstein's anomaly. Other morphologic characteristics of the normal right ventricle that should be noted include lack of atrioventricular–semilunar valve continuity, the presence of muscular conus, the existence of an infundibular or "outflow" portion of the ventricle, the presence of a moderator band, and poorly defined papillary muscles. In contrast, characteristic morphologic features of the left ventricle that are easily demonstrated with fetal echocardiography include atrioventricular–semilunar valve fibrous continuity, well-defined papillary muscles, and absence of a muscular conus. In fetal echocardiography, the most easily identified of these feaures is atrioventricular–semilunar valve continuity, which is seen to best advantage in the long-axis plane (Fig. 48–6).

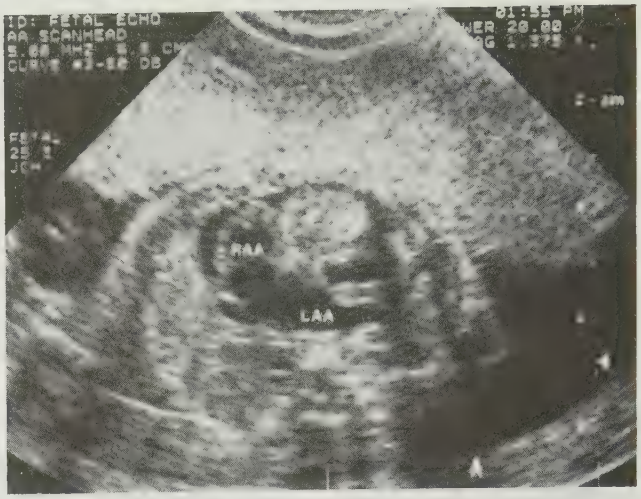

Fig. 48–2. Transverse plane of the fetal chest demonstrating characteristic right atrial appendage (RAA) and left atrial appendage (LAA) morphology in a fetus with atrial situs solitus. The left atrium lies immediately anterior to the fetal spine.

In addition to examination of the atrioventricular valves, the relative size of the ventricles can be assessed in the four-chamber plane. The left and right ventricle should appear to be approximately equal in size (Fig. 48–3). However, although right and left ventricular dimensions may be comparable,[19–22] analysis of ventricular geometry reveals a pattern of right ventricular dominance, which produces an elliptical left ventricular short axis in the fetus compared to the circular shape seen in infants and children.[23] Right ventricular enlargement is seen in some forms of pulmonary atresia with right ventricular dilation,[24] right ventricular

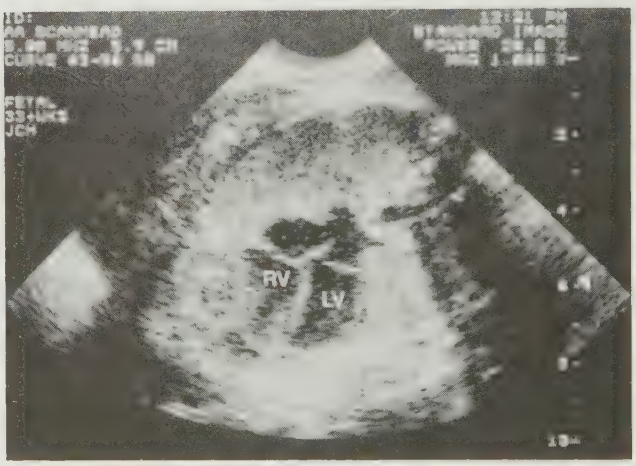

Fig. 48–3. Four-chamber view of a normal fetal heart seen in a transverse scan of the fetal chest. The apex is directed to the left, and the right ventricle (RV) and left ventricle (LV) are of approximately equal size. The septum primum is directed from the right atrium to the left atrium. The left atrium is immediately anterior to the aorta and fetal spine.

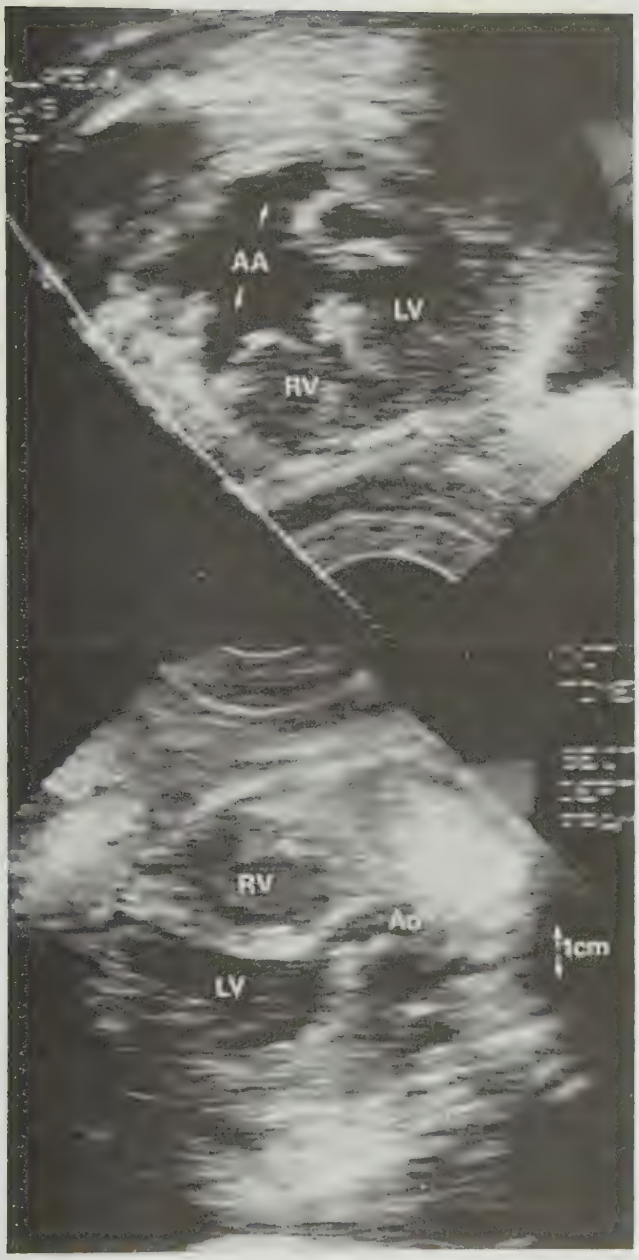

Fig. 48–4. The equivalent of a subcostal scan (upper panel) demonstrating a common atrium and common atrioventricular valve. The atrial appendage (AA) morphology suggests left atrial isomerism. In the long-axis scan (lower panel), the "gooseneck" deformity of the left ventricular outflow tract in atrioventricular canal defects is seen. In this fetus, there is narrowing of the left ventricular (LV) outflow tract and a small aortic root (Ao). RV = right ventricle.

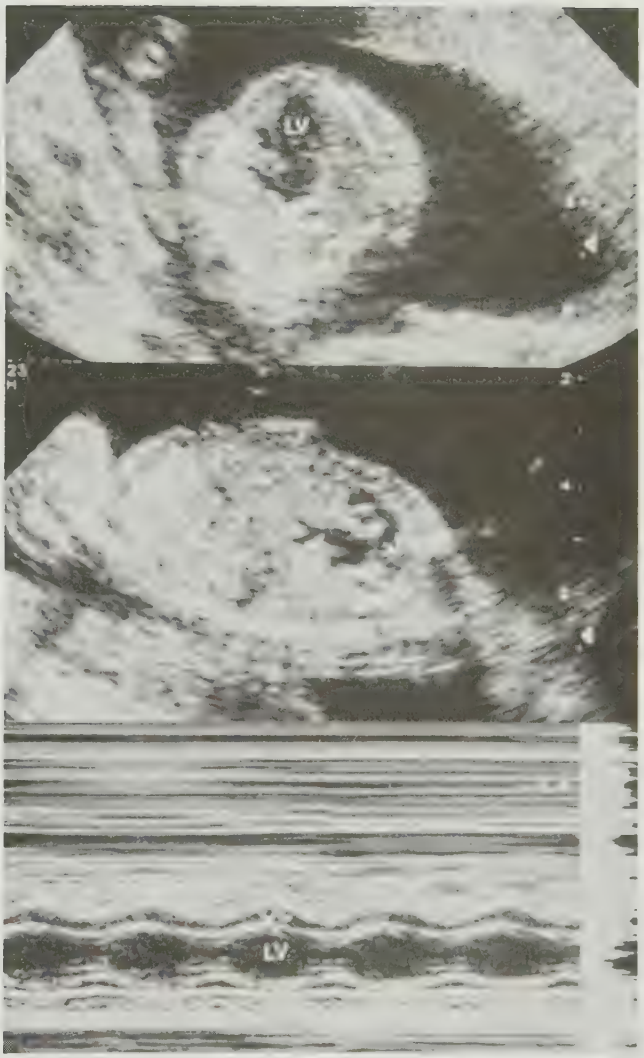

Fig. 48–5. Univentricular atrioventricular connection is demonstrated in the upper panel. A single atrioventricular valve connects to the left ventricle (LV) with a small, anterior, right ventricular outlet chamber (RVOC). Ventriculoarterial connection is concordant as demonstrated in the modified short-axis scan (middle panel). M-mode echocardiography (lower panel) also demonstrates a single ventricle with a small outlet chamber (OC). Ao = aorta; IVC = inferior vena cava; PA = pulmonary artery.

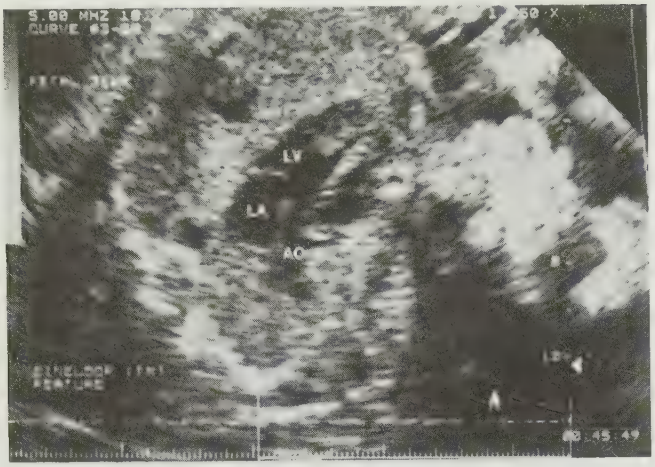

Fig. 48–6. Left ventricular (LV) morphology is established in the apical long-axis scan of a normal fetus. The mitral valve is in fibrous continuity with the aortic valve (AO) between the left atrium (LA) and left ventricle (LV). Demonstration of atrioventricular valve–semilunar valve fibrous continuity is the most useful morphologic characteristic for identifying the left ventricle in fetal echocardiography.

dominant atrioventricular canal, hypoplastic left heart syndrome,[25] coarctation of the aorta,[26] and nonimmune hydrops fetalis secondary to congestive heart failure[12] (Fig. 48–7). Enlargement of the left ventricle, usually in association with right ventricular enlargement, may be seen in critical aortic stenosis, endocardial fibroelastosis, cardiomyopathy, or congestive heart failure of undetermined cause[14] (Fig. 48–8).

The inlet ventricular septum is also best assessed in the four-chamber plane and easily demonstrates the inlet muscular ventricular septal defect and typical abnormal valve morphology of complete atrioventricular canal[12,14] (Fig. 48–9). In addition, septal hypertrophy and reduced cardiac function are demonstrable in fetuses of poorly controlled diabetics,[17] as well as those with a thick septum for other reasons (see Fig. 48–10). Naturally, absence of the ventricular septum or atresia of one or the other atrioventricular valve is characteristic of single ventricle with mitral or tricuspid atresia, single ventricle with common atrioventricular valve, and double-inlet left ventricle (Fig. 48–5). These congenital defects are usually readily apparent when adequate four-chamber imaging is obtained. Ventricular septal defects (Fig. 48–9 and Fig. 48–11) have been diagnosed in utero, although a false positive or false negative diagnosis of small ventricular septal defects is likely. Silverman and Golbus have observed closure of a ventricular septal defect during the course of gestation.[14]

After establishing atrioventricular connection and examining ventricular morphology and the ventricular septum, ventriculoarterial connection is established. This is accomplished by using a combination of long- and short-axis planes. Demonstration of a normal right ventricular outflow tract connecting to the pulmonary artery and ductus arteriosus is important to establish normal ventriculoarterial connection (Fig. 48–12). However, the pulmonary artery and ductus arteriosus may be easily mistaken for the ascending aorta and aortic arch because of the normal continuity of the ductus to the descending aorta. Careful demonstration of the aortic arch with brachiocephalic branches, which are usually readily identified, differentiates the aortic arch from the pulmonary artery and ductus arteriosus. In addition, the aortic arch courses more cephalad and is smaller than the ductus. In particular, the continuity of the aortic arch with the descending aorta, the aortic isthmus, is very small in the human fetus, in contrast to the ductus arteriosus, which is virtually equal in size to the descending aorta. Establishing connection of the aorta to the left ventricle with mitral/aortic continuity completes the picture of normal ventriculoarterial connection.

The normal appearance and function of the semilunar valves can be demonstrated by both two-dimensional and M-mode echocardiography. Demonstration of normal pulmonary valve size and function is useful in excluding pulmonary atresia. In patients with pulmonary atresia, in addition to abnormal pulmonary valve anatomy and motion, there is also hypoplasia of the main pulmonary artery and ductus arteriosus (Fig. 48–13) with relative enlargement of the ascending aorta. These patients also exhibit abnormalities of right ventricular size and function.[24] In tetralogy of Fallot, varying degrees of right ventricular outflow tract and pulmonary

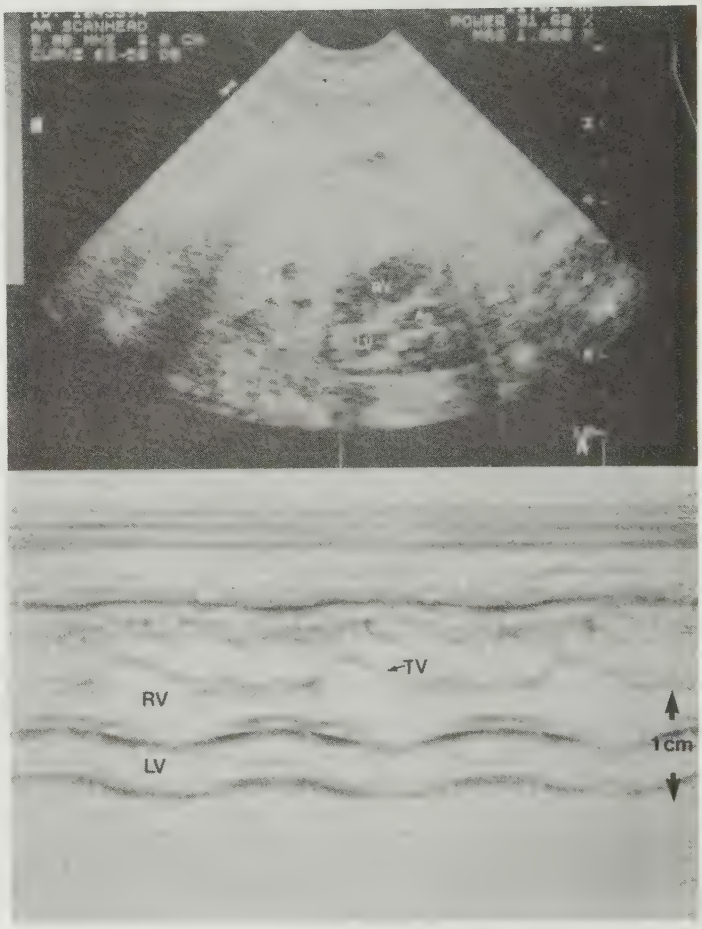

Fig. 48–7. Right ventricular (RV) enlargement and endocardial fibroelastosis of the left ventricle (LV) are demonstrated in both the two-dimensional (upper panel) and M-mode (lower panel) echocardiogram. Significant hypoplasia of the left ventricle and echodensity of the left ventricular endocardium are characteristic of critical aortic stenosis in affected fetuses. Mild poststenotic dilation of the aorta (Ao) can also be seen in the two-dimensional images (upper panel). TV = tricuspid valve.

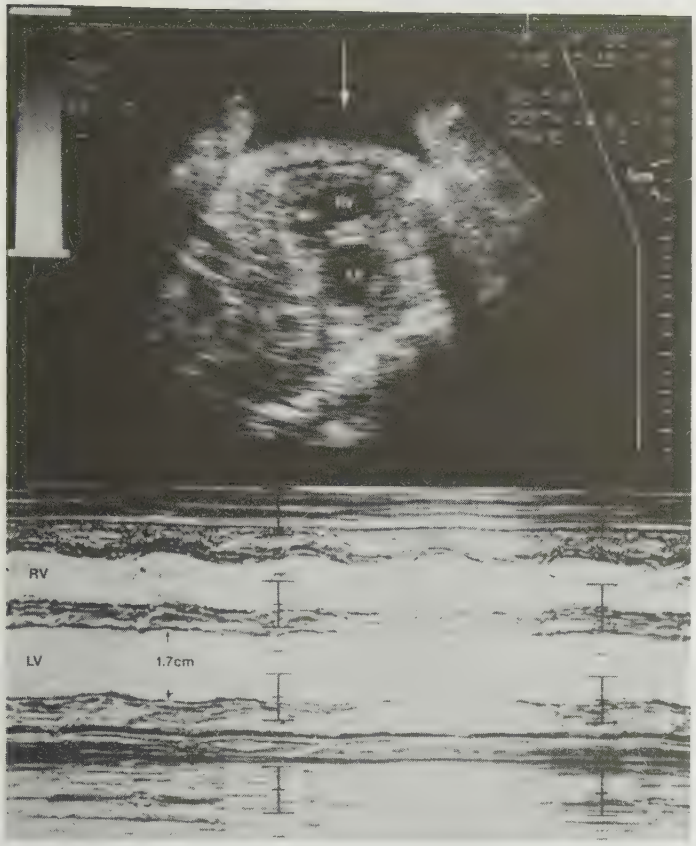

Fig. 48–8. Two-dimensional (upper panel) and M-mode (lower panel) echocardiogram in a 32-week fetus with cardiomyopathy. A small pericardial effusion is visible in the two-dimensional image. The left ventricle (LV) is enlarged, and the left ventricular posterior wall motion is abnormal. Although the right ventricle (RV) is mildly enlarged on the two-dimensional echocardiogram, the left ventricle is more severely affected by M-mode, a finding that implies ventricular myocardial disease.

hypoplasia are observed in addition to a large ventricular septal defect with a large overriding aorta.[12] Conversely, in aortic atresia, extreme hypoplasia of the ascending aorta and aortic arch is observed in addition to gross right ventricular enlargement[15] with enlargement of the main pulmonary artery and ductus. Lesions that produce aortic arch obstruction, such as coarctation of the aorta or interrupted aortic arch, should be suspected in any fetus with right ventricular enlargement but without evidence of proximal aortic obstruction.[26] Actual demonstration of aortic coarctation or interruption is difficult because of the small size of the aortic isthmus in the normal fetus; therefore aortic coarctation is one of the most difficult diagnoses to make on fetal ultrasound. However, on fetal examination, the appearance of the characteristic hypoplasia of the transverse arch and enlargement of the pulmonary artery observed in neonates with isolated coarctation should alert the fetal ultrasonographer to the possible existence of an aortic coarctation. Critical aortic stenosis (Fig. 48–14) can be recognized by the presence of a small aortic anulus; poststenotic dilation of the ascending aorta; abnormal aortic valve morphology, left ventricular dilation, hypertrophy, or hypoplasia; and endocardial fibroelastosis.[27,28]

The spectrum of cardiac anomalies that may be detected in utero is considerably different from the spectrum of defects that are observed in postnatal life.[14,24,29] The indications for referral to a specialist for fetal cardiac ultrasound will lead to a greater proportion of fetuses affected by severe congenital anomalies that produce fetal congestive heart failure and hydrops, fetal arrhythmia, or abnormal ventricular or atrioventricular valve morphology detected on routine obstetric ultrasound. Because of the route of the fetal circulation, some of the more common defects of postnatal life cannot be detected in utero, such as secundum atrial septal defects and patent ductus arteriosus. Other common postnatal defects are diagnosed with difficulty in utero, such as small ventricular septal defects and coarctation of the aorta, or are recognized only in their most severe forms, such as pulmonary or aortic stenosis. The addition of pulsed Doppler, in either the conventional or color flow format, to the two-dimensional echocardiographic examination may improve accuracy of diagnosis in milder degrees of semilunar valve stenosis or in patients with complex lesions.

Fig. 48–9. Transverse scan of the fetal chest demonstrating dextrocardia in a fetus with complete atrioventricular canal. The ventricular apex is directed to the right (upper panel). A common atrium, common atrioventricular valve orifice (CAVO), and inlet ventricular septal defect (arrow, lower panel) are demonstrated. The descending aorta (DAo) is to the left of the fetal spine. Mild ascites and a small pericardial effusion are also visible. RV = right ventricle; LV = left ventricle.

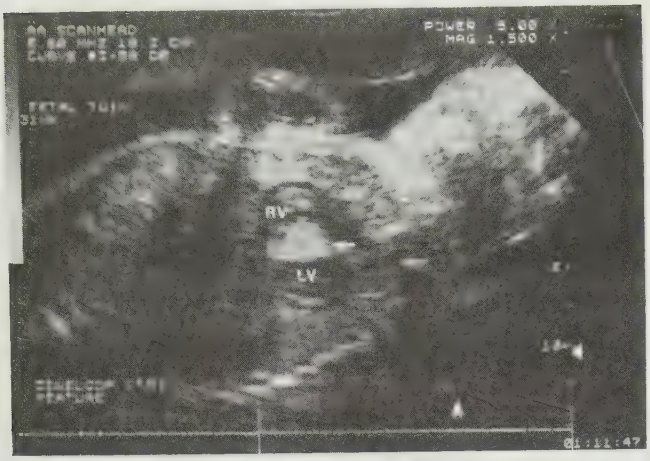

Fig. 48–10. Two-dimensional echocardiogram in the short-axis plane demonstrating significant thickening and echodensity (arrow) of the interventricular septum (IVS) in a 31-week fetus of a nondiabetic twin pregnancy. The right ventricle (RV) and left ventricle (LV) are of approximately equal size without hypertrophy of the ventricular free wall. The septal mass extends into the atrial septum and probably represents a septal rhabdomyoma.

As a rule, in the majority of cases, those defects that have the greatest effect on fetal and perinatal morbidity and mortality may be recognized in utero in most affected patients, allowing rational prenatal and postnatal intervention.

EVALUATION OF FETAL HEART RATE AND RHYTHM

As was noted above, with increased use of antepartum fetal heart rate monitoring, an increasing number of patients are being referred for evaluation of abnormalities of fetal heart rate and rhythm. It appears that abnormalities of heart rate and rhythm occur in only a small number of normal pregnancies. Southall and associates[30] have noted transient bradycardia in 1.1 to 1.3% of normal pregnancies and transient tachycardia in less than 1%. Premature contractions occur with only a slightly higher prevalence in fetuses than in neonates, being present in 1.7% of normal fetuses. Although abnormalities of heart rate and rhythm are uncommon and usually transient in normal pregnancies, patients undergoing antenatal heart rate monitoring as a means of assessing fetal well-being may be noted to have bradycardia, tachycardia, or an irregular rhythm. Unfortunately, fetal electrocardiograms are difficult to interpret because of the absence of fetal P waves, extraneous electrical noise, and the inability to recognize changes in QRS morphology. Nonetheless, accurate diagnosis and treatment of fetal arrhythmia are important to avoid unnecessary cesarian section or fetal death. Fetal echocardiography has been proven to be useful in the accurate diagnosis of fetal arrhythmia in the majority of cases. With this method, the electrical activation sequence of the atria and ventricles is inferred from the mechanical events detected by echocardiography.

Although a normal activation sequence may be recognized by two-dimensional echocardiography alone, accurate rhythm diagnosis requires the use of either two-dimensionally directed M-mode echocardiography[31–36] or duplex pulsed Doppler echocardiography.[35,36] A careful two-dimensional echocardiographic examination of the fetus is important to establish the presence or absence of congenital heart disease or cardiac failure. The latter is manifested by cardiac enlargement and fetal hydrops. The nature of the rhythm disturbance can then be established by either M-mode or Doppler echocardiography.

M-Mode Echocardiography

In using M-mode echocardiography, the line of M-mode interrogation is directed by two-dimensional imaging through both atrial and ventricular structures, such as atrial and ventricular wall, through the aortic root and left atrium, or through an atrioventricular valve. In this way, atrial contraction is established by atrial wall motion or an A wave of the atrioventricular valve.[31–36] Ventricular contraction is recognized by ventricular wall motion, closure of the atrioventricular valve, or opening of arterial valves. An irregular rhythm is the most common reason for referral for diagnosis of fetal arrhythmia. The irregular rhythm is almost always the result of premature contractions followed by a pause. Premature contractions preceded by atrial wall motion or an early A wave are premature atrial contractions (Fig. 48–15). Ventricular premature contractions are characterized by early ventricular wall

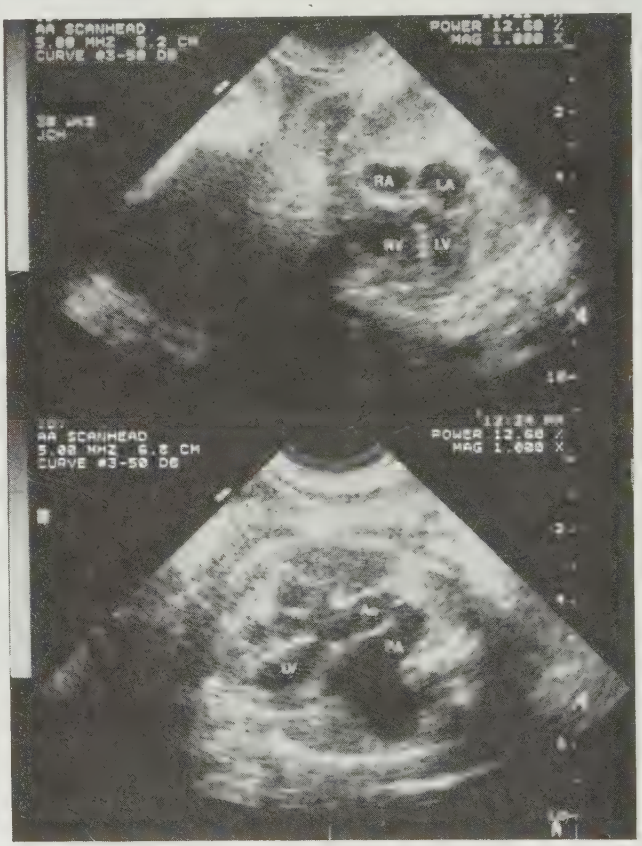

Fig. 48–11. Aortic override of a ventricular septal defect in a fetus with absent pulmonary valve syndrome. In the upper panel, the ventricular septal defect is easily seen in a four-chamber scan of the fetal heart. In a modified long-axis scan (lower panel), the aorta overrides the ventricular septal defect with marked enlargement of the pulmonary artery. RV = right ventricle; LV = left ventricle; Ao = aorta; PA = pulmonary artery; RA = right atrium; LA = left atrium.

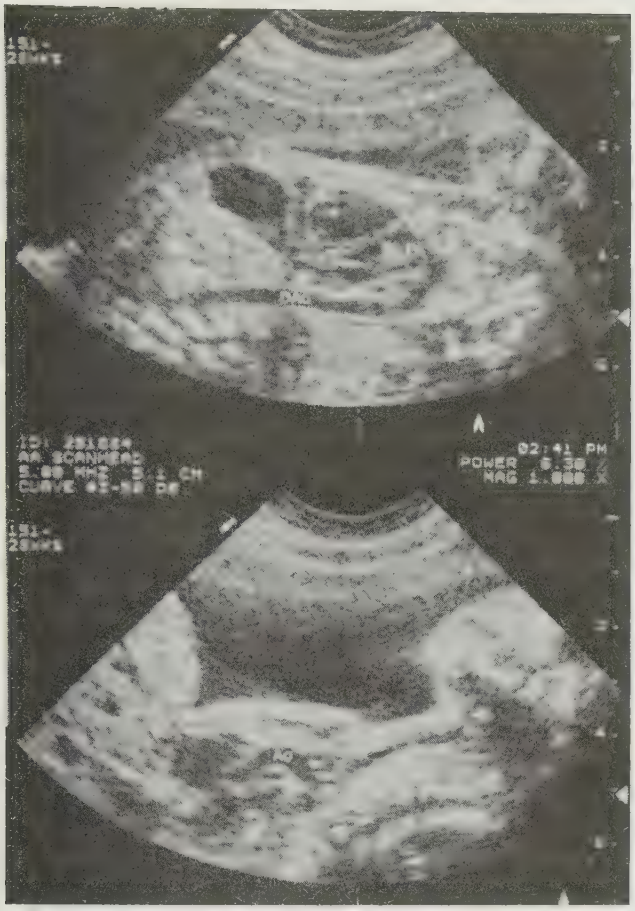

Fig. 48–12. Normal ventriculoarterial connection is established by demonstrating connection of the pulmonary artery (PA) to the right ventricle (upper panel) and of the aorta (Ao) to the left ventricle (lower panel). The pulmonary artery is identified by branching of the right and left pulmonary arteries and ductus arteriosus. The aorta is identified by branching of the brachiocephalic vessels. DAo = descending aorta.

motion or atrioventricular valve closure without evidence of a preceding atrial contraction. Rarely, mixed premature atrial and ventricular contractions occur in the same patient.[31,33]

Fetal bradycardia, defined for purposes of arrhythmia diagnosis as a sustained heart rate below 100 beats per minute, is usually sinus bradycardia with evidence of atrial contraction preceding each ventricular contraction. The discussion that follows is limited to fetal bradycardia not associated with labor and does not include discussion of characteristic patterns of sinus bradycardia associated with fetal distress during parturition. Sinus bradycardia noted during echocardiographic examination is most often transient and may be the result of transducer pressure on the maternal abdomen.[35] Another cause of fetal bradycardia that may be mistaken for complete AV block is blocked premature atrial contractions or blocked atrial bigeminy. Blocked premature atrial contractions are represented by early atrial wall motion or A wave without subsequent ventricular contraction followed by a pause in atrial contraction. In contrast to complete AV block, blocked premature atrial bigeminy is characterized by an irregular atrial rate and an atrial contraction preceding every other ventricular contraction. In complete AV block, atrial contraction occurs without relation to ventricular contraction and with ventricular bradycardia. In complete AV block, M-mode echocardiography reveals A waves "marching through" regular atrioventricular valve closure or atrial wall motion without relation to ventricular wall motion. Ventricular rates in complete AV block usually range from 60 to 80 beats per minute. Second-degree AV block with fixed or variable ratios of atrioventricular conduction may also be recognized by M-mode echocardiography (Fig. 48–16). It is important to establish the mechanism of fetal bradycardia before instituting therapy. Unnecessary cesarean section has resulted from assuming that fetal bradycardia was secondary to fetal distress and failing to recognize complete AV block or blocked premature atrial contractions.

Supraventricular tachycardia is characterized by atrial rates above 180 beats per minute with atrial contractions or A waves usually preceding each ventricular contraction (Fig. 48–15). This rhythm cannot be distinguished by echocardiography from ventricular tachycardia with 1:1 retrograde conduction to the atrium. However, many cases of supraventricular tachycardia diagnosed and treated in utero have recurred in the neonatal period, allowing confirmation of the in utero echocardiographic diagnosis. There

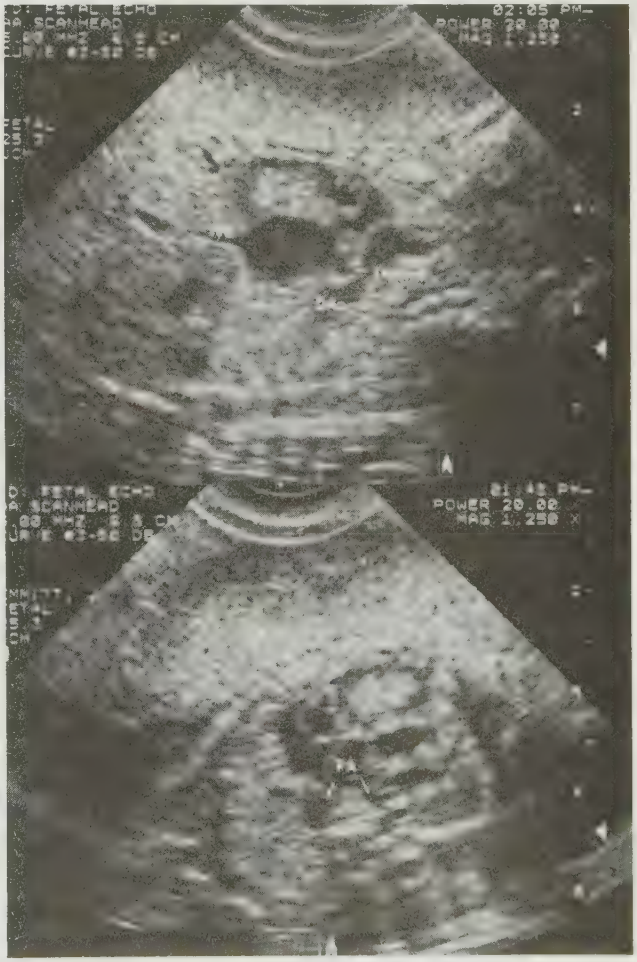

Fig. 48–13. A small serpiginous ductus arteriosus in a fetus with pulmonary atresia demonstrated in the upper panel. In the lower panel the small right and left pulmonary arteries are visible. PA = pulmonary artery; Ductus = ductus arteriosus; IVC = inferior vena cava.

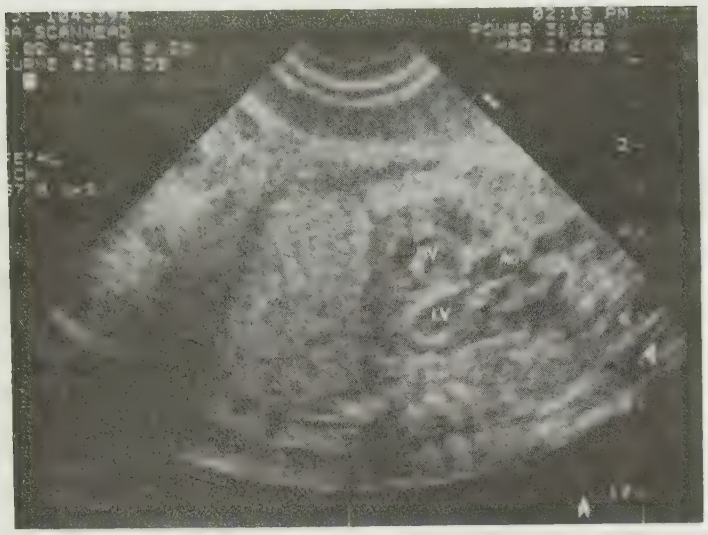

Fig. 48–14. Modified long-axis scan of a fetus with critical aortic stenosis. Echodensity of the left ventricular (LV) endocardium, poststenotic dilation of the aorta (Ao), and right ventricular (RV) enlargement are characteristic of this lesion in the fetus and neonate.

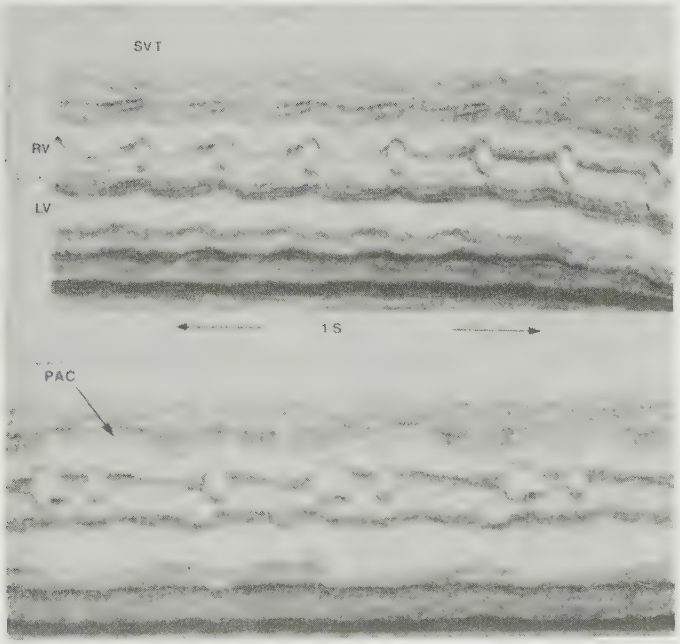

Fig. 48–15. M-mode echocardiograms in supraventricular tachycardia (upper panel) and sinus rhythm with premature atrial contractions (lower panel). In supraventricular tachycardia (SVT), separate tricuspid valve E and A waves are not visible because of the rapid atrial rate. In contrast, during sinus rhythm separate E and A waves are easily seen. The premature opening of the tricuspid valve (arrow) in the lower panel occurs as the result of a premature atrial contraction (PAC) occurring immediately following ventricular systole. This is followed by an atrial pause. RV = right ventricle; LV = left ventricle.

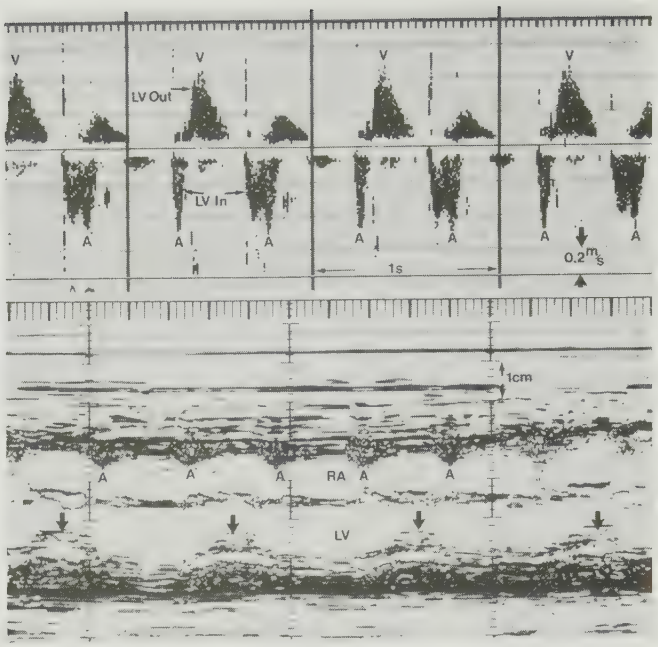

Fig. 48–16. Comparison of Doppler (upper panel) and M-mode (lower panel) echocardiograms in a fetus with 2:1 AV block. The Doppler recording from the left ventricular (LV) inlet demonstrates inflow (LV In) and outflow (LV Out) in opposite directions. A waves (A) produced by atrial systole occur at regular intervals with a 2:1 relationship to ventricular systole (V). In the M-mode echocardiogram, right atrial (RA) wall motion occurs with a 2:1 relationship to left ventricular wall (LV) motion (arrows). m/s = meters per second; s = second.

have been only a few cases of ventricular tachycardia that was incorrectly diagnosed as supraventricular tachycardia in utero. Atrial flutter is recognized by M-mode echocardiography by very high rates of atrial contraction, usually above 400 beats per minute. Variable ratios of AV block are observed with atrial flutter. Atrial contraction is followed by ventricular contraction in ratios of 2:1 to 4:1 in the majority of cases.

Doppler Echocardiography

Doppler echocardiography may be used to diagnose fetal arrhythmia with an accuracy equal to that of M-mode echocardiography.[36] The basic principle is to deduce the activation sequence from the sequence of flow detected by range-gated pulsed Doppler. Sampling of atrioventricular valve flow or foramen ovale flow allows description of the pattern of atrial contraction, whereas sampling of left ventricular outflow tract or arterial flow allows description of the pattern of ventricular contraction (Fig. 48–17). Doppler interrogation of the left ventricular inlet usually allows simultaneous description of atrioventricular valve and left ventricular outflow tract flow, thus allowing description of the activation sequence by sampling in one location. Sinus rhythm and sinus bradycardia are characterized by an atrial A wave preceding each systolic velocity profile (Fig. 48–18). Premature atrial contractions are characterized by early occurrence of the A wave, by accentuation of peak atrioventricular valve velocity, or by early accentuation of peak velocity through the foramen ovale. The early atrial flow is followed by ventricular flow of lower velocity than the preceding sinus beat. Prolonged passive ventricular filling and

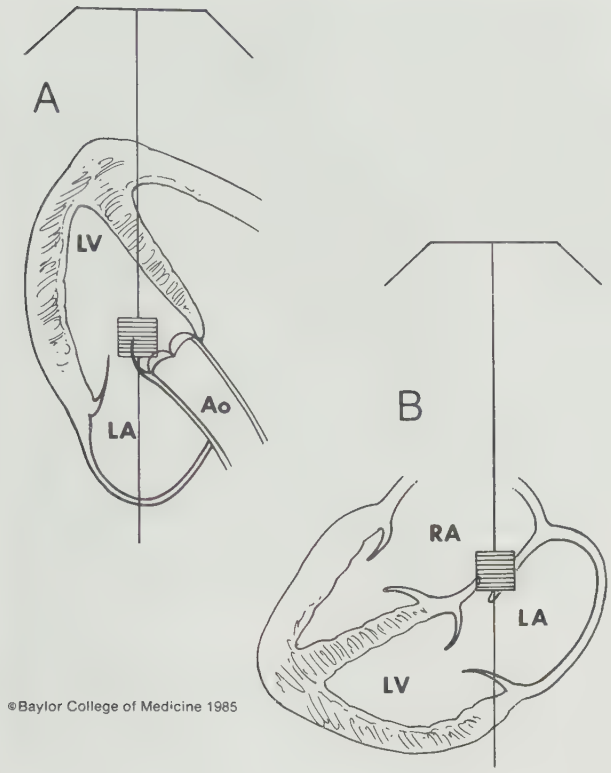

Fig. 48–17. Illustration of Doppler sample volume positions (a) in the left ventricular (LV) inlet to record left ventricular diastolic inflow and systolic outflow and (b) in the foramen ovale to record atrial systole. LA = left atrium; RA = right atrium; Ao = aorta. (From Strasburger, J.F., et al.: Doppler echocardiography in the diagnosis and management of persistent fetal arrhythmias. J. Am. Coll. Cardiol., 7:1386, 1986.)

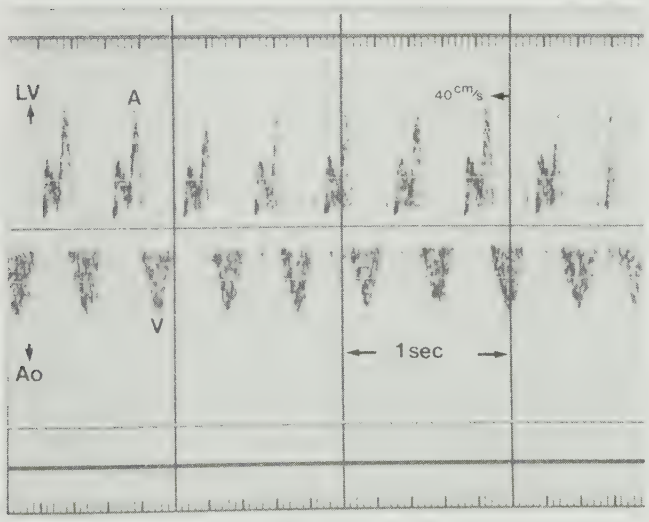

Fig. 48–18. Left ventricular (LV) inflow and outflow recorded in sinus rhythm from the left ventricular inlet. Atrial systole (A) follows passive filling and is greater in amplitude in the fetus. Ventricular systole (V) follows each atrial systole, documenting a normal activation sequence. Ao = aorta.

accentuation of ventricular flow velocities (postextrasystolic potentiation) occur following an atrial pause. Early atrial flow may not be followed by ventricular flow if AV block occurs (Fig. 48–19). With premature ventricular contractions, early venticular systole causes abbreviation of atrioventricular valve flow associated with early ventricular flow of lower velocity than the preceding normal beat (Fig. 48–20). There may be associated systolic atrioventricular valve insufficiency (Fig. 48–21). With premature ventricular contractions, a pause is observed with prolonged passive ventricular filling and accentuated ventricular velocities on the beat following the premature contraction.

Complete AV block is characterized by an atrial A wave that is dissociated from ventricular or arterial flow (Fig. 48–22). Diastolic atrioventricular valve insufficiency, produced by failure of atrioventricular valve closure following atrial systole, may be observed in some patients with complete AV block (Fig. 48–23). As with M-mode echocardiography, atrial bigeminy can be distinguished from complete AV block by the presence of early atrial flow without subsequent ventricular flow alternating with 1:1 atrial and ventricular flow. In supraventricular tachycardia and atrial flutter, rapid atrial contraction produces low-amplitude atrial A waves that merge with passive atrial filling followed by low-amplitude ventricular flow. Rapid atrial contraction may also be demonstrated by pulsed Doppler sampling in the foramen ovale (Fig. 48–24). Although atrial flutter with 1:1 conduction and supraventricular tachycardia may not be distinguished by Doppler echocardiography, atrial flutter usually occurs with atrial rates of 400 beats per minute or more and is usually associated with AV block (Fig. 48–25). Supraventricular tachycardia is more likely to occur at rates of 200 to 300 beats per minute with 1:1 atrioventricular conduction.

By using the echocardiographic methods described above, the spectrum and outcome of fetal arrhythmias have been described.[31–36] By far the most frequent arrhythmias observed in the fetus are isolated premature contractions. In most studies, the great majority of premature contractions are atrial in origin.[31–34,36] Although occasional patients with premature atrial contractions develop supraventricular tachycardia, the majority experience resolution of premature contractions either in utero or early in their neonatal course. Premature ventricular contractions, although uncommon, appear to have a similarly benign prognosis. Transient bradycardia to rates below 100 beats per minute is not uncommonly observed and may result from fetal movement[33] or transducer pressure.[35] As was noted above, sustained bradycardia, defined as a heart rate persistently below 100 beats per minute, may be due to sinus bradycardia and fetal distress, blocked atrial bigeminy, or complete AV block. Complete AV block is associated with maternal autoimmune disease in the majority of cases.[31,33] When associated congenital heart disease is present, complex anomalies are usually observed, most often involving right or left atrial isomerism with common atria, common atrioventricular valve, and abnormal systemic venous return.[31–33,36,37] Recognition of complete AV block in the fetus should lead to a thorough search for associated cardiac defects or maternal autoimmune disease. Likewise, patients with fetal AV block should be observed at frequent intervals for the development of signs of hydrops. The ultimate prognosis for fetuses with complete AV block and hydrops is poor. Successful transabdominal fetal ventricular pacing has been performed in a hydropic previable human fetus[37] and should be con-

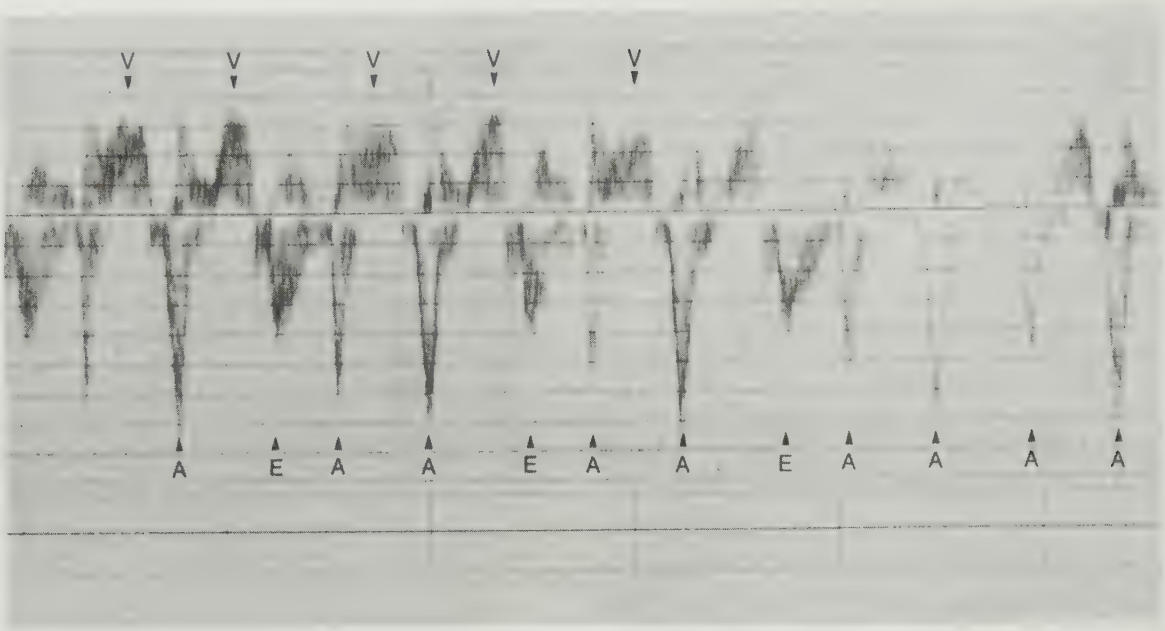

Fig. 48–19. Atrioventricular contraction sequence is recorded here by pulsed Doppler sampling in the left ventricular outflow tract. Atrial bigeminy is demonstrated by accentuation of the A wave (A) during diastole followed by a compensatory pause and prolonged passive filling (E). Each atrial contraction is followed by a ventricular systole (V). After a sequence of atrial bigeminy, a series of three premature atrial contractions occurs.

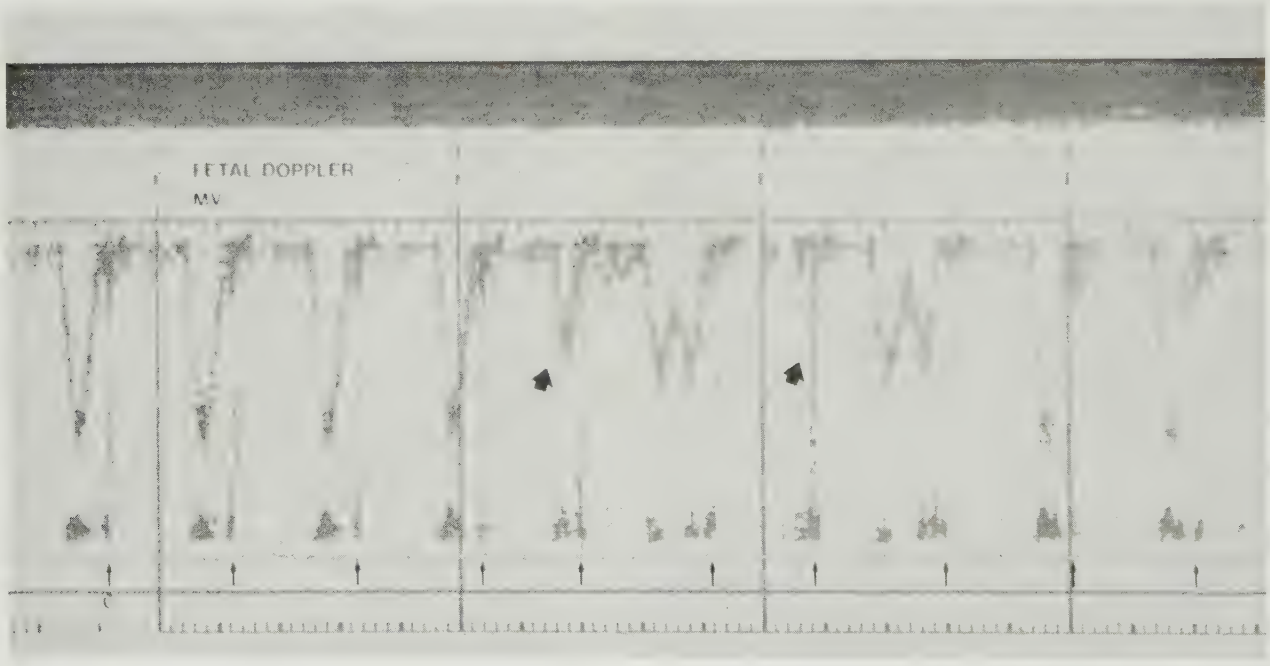

Fig. 48–20. Doppler sampling in premature contractions, probably junctional or ventricular. Early mitral valve (MV) closure (arrows) attenuates left ventricular filling with a compensatory pause. The latter occurs as a result of retrograde conduction of the premature junctional or ventricular contraction to the atrium. Because of the compensatory pause, separate E and A waves are visible during the diastolic period following the premature contraction.

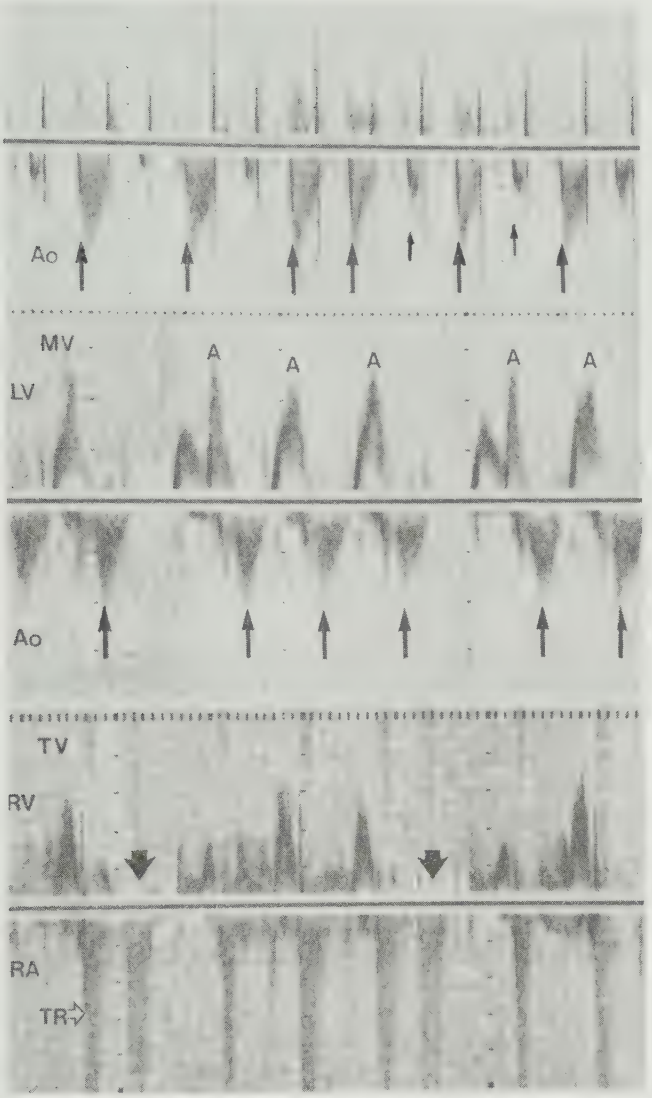

Fig. 48–21. A series of premature contractions are demonstrated by Doppler sampling of aortic (Ao) flow (upper panel), left ventricular inflow and outflow (middle panel), and tricuspid valve flow (lower panel). Frequent premature contractions result in varying amplitude of aortic velocities, which occur at irregular intervals (upper panel). The nature of the rhythm disturbance cannot be determined from aortic sampling. Doppler sampling in the left ventricular (LV) inlet (middle panel) reveals the complex nature of the arrhythmia. Mitral valve (MV) velocities are recorded on the first diastole and are followed by ventricular systole (arrow). Following ventricular systole, however, mitral valve opening does not occur. After a pause, mitral opening occurs with both passive filling and atrial systole. Following a series of three atrial and ventricular systoles, failure of mitral valve opening occurs again but without a corresponding ventricular systole. Doppler sampling in the tricuspid valve (TV) orifice (lower panel) reveals the true nature of the premature contractions. The presence of tricuspid regurgitation (TR) in the right atrium (RA) allows differentiation of systolic and diastolic events. Early occurrence of tricuspid regurgitation (dark arrows in the lower panel) immediately following ventricular systole is the result of very early premature junctional or ventricular contractions. This results in atrioventricular valve closure but produces only trivial systolic aortic flow (upper panel).

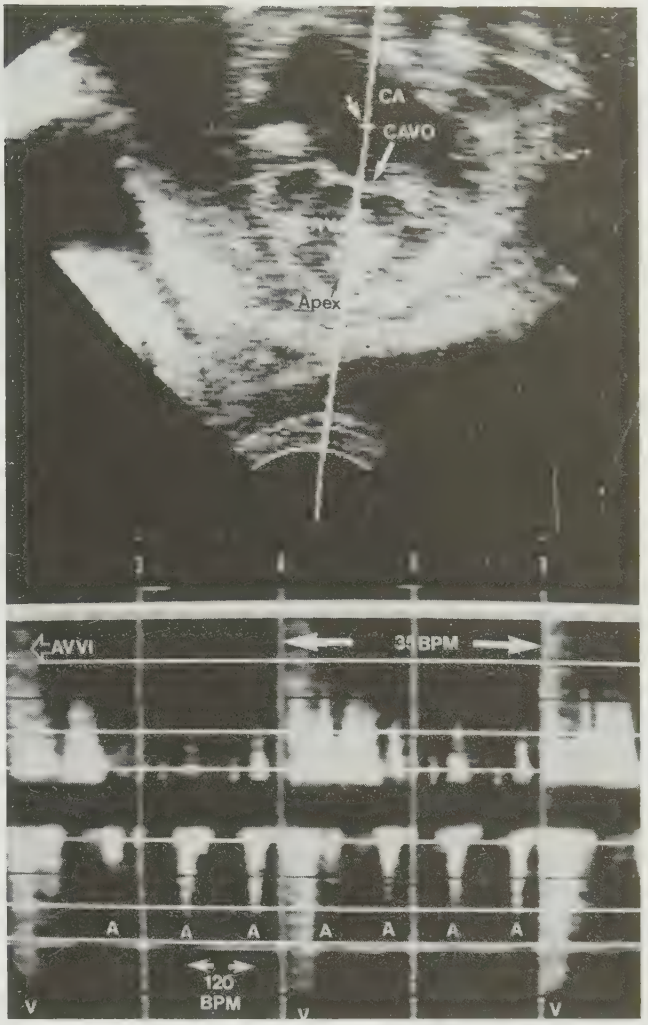

Fig. 48–22. Complete AV block is demonstrated by pulsed Doppler sampling in the common atrium (CA) of a 24-week fetus with complete atrioventricular canal and left atrial isomerism (upper panel). Regular atrial systole (A) occurs at a rate of 120 beats per minute (BPM). Ventricular systole (V) is recognized by high-velocity atrioventricular valve insufficiency (AVVI) at a rate of 35 beats per minute. Atrial systole and ventricular systole are dissociated. CAVO = common atrioventricular valve orifice; RV = right ventricle.

sidered in fetal patients with inadequate pulmonary maturity to sustain life. If pulmonary maturity is adequate, early delivery by cesarean section should be performed for the patient with complete AV block and progressive development of nonimmune hydrops fetalis.

Sustained tachycardia, defined as a heart rate persistently greater than 180 beats per minute, is usually caused by either supraventricular tachycardia or atrial flutter. Supraventricular tachycardia is the cause of sustained fetal tachycardia in 50 to 80% of cases,[31–36] atrial flutter accounting for the most of the remaining cases. Patients with fetal supraventricular tachycardia or atrial flutter should be hospitalized for medical treatment. With supraventricular tachycardia, the response to medical treatment is good even in some patients with fetal hydrops. However, early delivery following

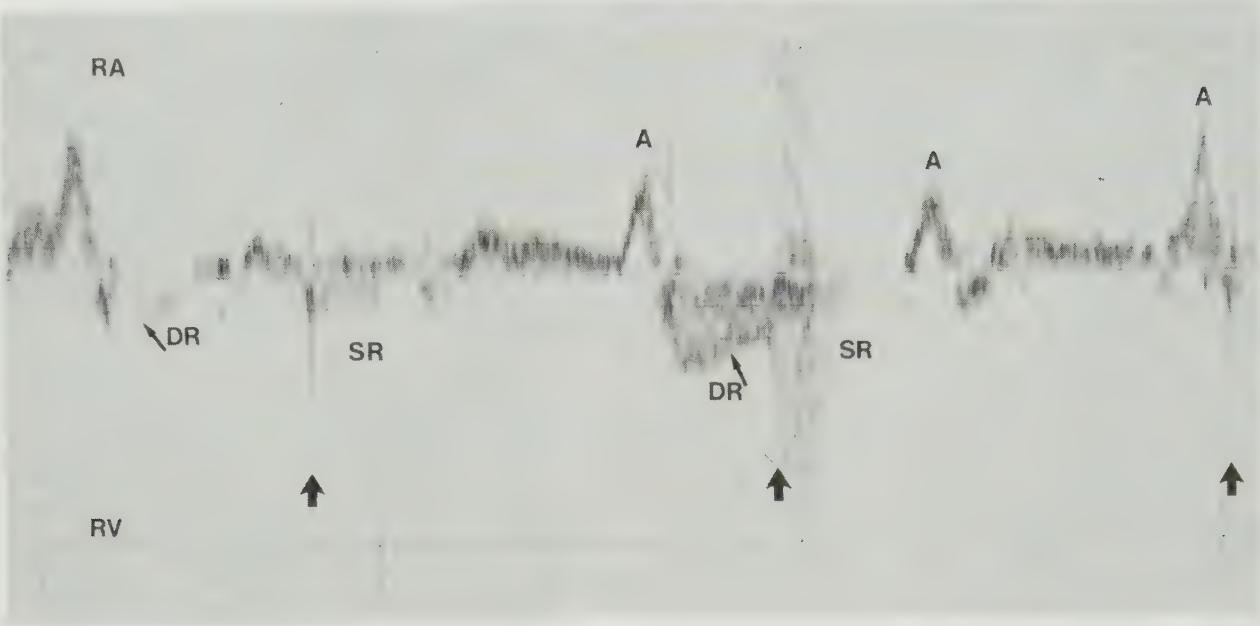

Fig. 48–23. Doppler recording of diastolic atrioventricular valve regurgitation (DR) occurring as a result of delayed closure of the tricuspid valve in a fetus with complete AV block. Systolic regurgitation (SR) marks the occurrence of ventricular systole (arrow), which is dissociated from atrial systole (A). RA = right atrium; RV = right ventricle.

assessment of pulmonary maturity should be considered for patients with sustained tachycardia when medical therapy fails and signs of hydrops become progressive.[34]

EVALUATION OF FETAL CIRCULATORY FUNCTION

Cardiac dysfunction in the fetus may result from a variety of causes, only some of which are primarily cardiac in origin. The first and major manifestation of cardiac failure noted by the obstetrician is often hydrops fetalis.[12] Nonimmune hydrops fetalis may be the initial manifestation of cardiac failure in a variety of clinical settings, including maternal anemia, pre-eclampsia, and polyhydramnios.[38] Cardiac enlargement is often noted in hydropic fetuses, regardless of the cause, and disproportionately affects the right ventricle. This is probably because the right ventricle provides the majority of fetal blood flow ultimately supplying the placenta. Congenital anomalies are frequently encountered in the fetus with nonimmune hydrops, only a minority of which are cardiac defects.[38,39] However, nonimmune hydrops appears to be much more likely to occur if the congenital anomalies that are present include malformation of the heart. Hydrops frequently intervenes when fetal arrhythmias are not successfully controlled in utero.[12,14,31,37] In addition to cardiac enlargement, other indices of reduced cardiac function may be present. After excluding fetal arrhythmia and cardiac defects, the echocardiographic assessment of heart size and function is an important part of the evaluation of the fetus with hydrops. Assessment of heart function using two-dimensional, M-mode, and Doppler echocardiography is described below.

Two-Dimensional and M-Mode Echocardiography

Disparities in cardiac chamber size often provide strong evidence of congenital heart disease or abnormal cardiac function in

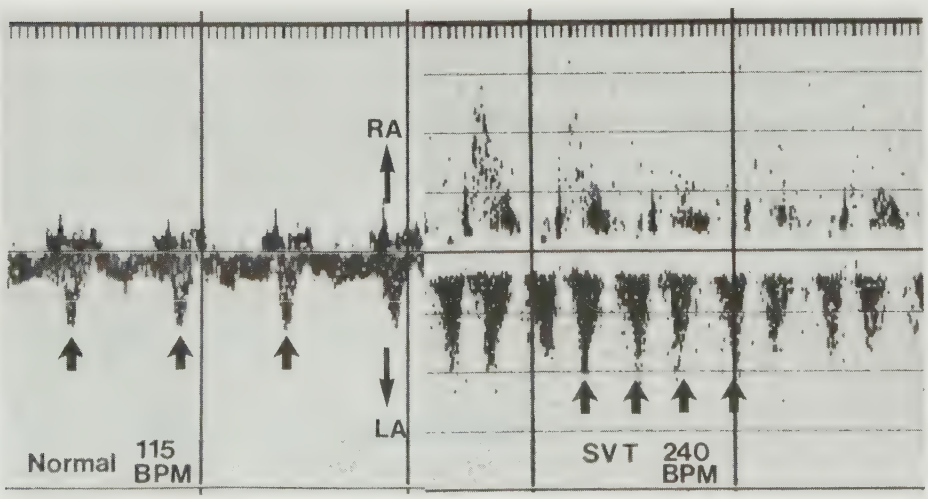

Fig. 48–24. Atrial systole recorded by pulsed Doppler sampling in the foramen ovale. On the left, in normal sinus rhythm, atrial systole (arrow) occurs at a rate of 115 beats per minute (BPM). On the right, atrial systole occurs at 240 beats per minute in a 28-week fetus with supraventricular tachycardia (SVT). RA = right ventricle; LA = left atrium.

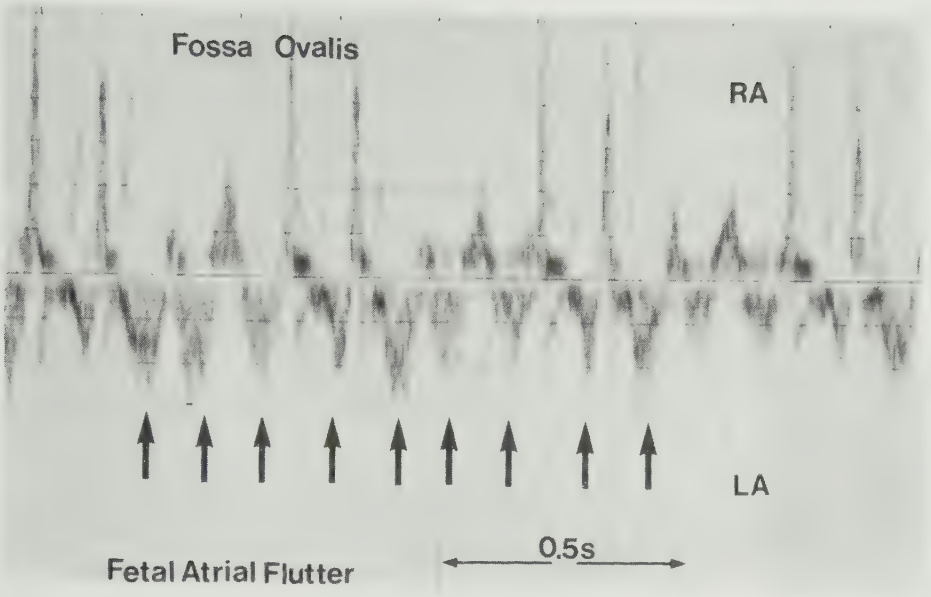

Fig. 48–25. Atrial flutter recorded by Doppler sampling in the fossa ovalis. Atrial systole (arrow) occurs at approximately 480 beats per minute. RA = right atrium; LA = left atrium. s = second.

the fetus. In comparison of right and left ventricular size, one ventricle may appear larger than the other (Figs. 48–7 and 48–8). However, without an appreciation of normal cardiac chamber size in the fetus, it would be difficult to determine whether one ventricle was enlarged, the other was unusually small, or both.

In two-dimensional echocardiographic scanning of the normal human fetus, at any gestational age, the right and left ventricles should be of approximately equal size in the four-chamber and short-axis scans (Fig. 48–26). A number of studies using both two-dimensional and M-mode echocardiography have established normal ventricular size in the human fetus.[19–23,40] However, a variety of methods have been employed in obtaining measurements of fetal ventricular size that have led to some variation in the results of investigators. In addition, since synchronization of the M-mode recording with the electrocardiogram is not possible with fetal echocardiography, standard methods of measurement of ventricular diastolic dimensions cannot be employed. The comparison of ventricular size and shortening fraction in the fetus to the same parameters in the neonate is not possible because of the presence of paradoxical or flat septal motion in the fetus and differences in ventricular geometry before and after birth. This is presumably the result of the relative volume loading of the right ventricle in utero.[20,23] Normal values in the fetus may be related to estimated fetal gestational age, estimated fetal weight, or fetal parameters of growth such as biparietal diameter, abdominal circumference, or femur length. Despite differences in methodology, the results of these studies provide useful parameters that may aid in the diagnosis of chamber enlargement or dysfunction.

Sahn and associates[22] have described the changes in ventricular and great vessel size with increasing gestational age in fetuses of greater than 20 weeks gestation using measurements obtained with two-dimensional echocardiography. Measurements of ventricular dimension were taken from four-chamber views at the level of the atrioventricular valves and immediately prior to atrioventricular valve closure. Great vessel dimensions were recorded from short-axis views. Values were related to estimated fetal weight. A curvilinear relationship was found between estimated fetal weight and ventricular diameter and between estimated fetal weight and great vessel diameter. The mean ratio of right ventricular diameter to left ventricular diameter was 1.2:1, and the ratio of pulmonary artery to aortic diameter was approximately 1.2:1. Wladimiroff and associates[20] studied fetuses of greater than 28 weeks gestation using two-dimensionally directed M-mode of both ventricular chambers in the four-chamber view. Parameters were related to estimated gestational age. End-diastole was defined as the point of maximum dimension of the ventricles, and end-systole as the minimum dimension. Left and right ventricular end-diastolic dimensions ranged from approximately 11 mm at 28 weeks to 18 mm at 40 weeks. End-systolic dimensions for both ventricles ranged from 8 mm at 28 weeks to 14 mm at term. Thus the ratio of right ventricular to left ventricular dimensions was consistently 1:1. Ventricular diameters increased linearly with increasing gestational age.[41] A longitudinal study by St. John Sutton and associates[21] was performed in 16 normal fetuses from 20 weeks to term. Two-dimensionally directed M-mode recordings were obtained at the level of the atrioventricular valves. Values were related to gestational age calculated from date of the last menstrual cycle and biparietal diameter. Right ventricular to left ventricular dimensions were comparable throughout gestation, increased linearly, and yielded a ratio of 0.96:1. Somewhat lower mean values for chamber dimensions were obtained in this study than in the study by Wladimiroff and associates, with an internal ventricular diameter at 20 weeks of 7 mm + 1 mm and at term of 15 mm + 2 mm. Left ventricular, right ventricular, and septal thickness were comparable and increased linearly throughout gestation. Maximum systolic wall thickness was 3 mm, and minimum thickness was 2 mm at 20 weeks gestation, increasing to 4.5 mm in systole and 3.5 mm in diastole at term. Similar results for chamber dimensions have been obtained by Devore and associates[19] and Allan and associates.[40] Devore and associates[19] found a linear relationship between ventricular diameters and biparietal diameter with a mean ratio of right ventricular diameter to left ventricular diameter of 1:1.

It is clear that the right and left ventricles are of approximately equal transverse diameter throughout gestation. However, this does not imply equal ventricular volume or equal stroke volume.

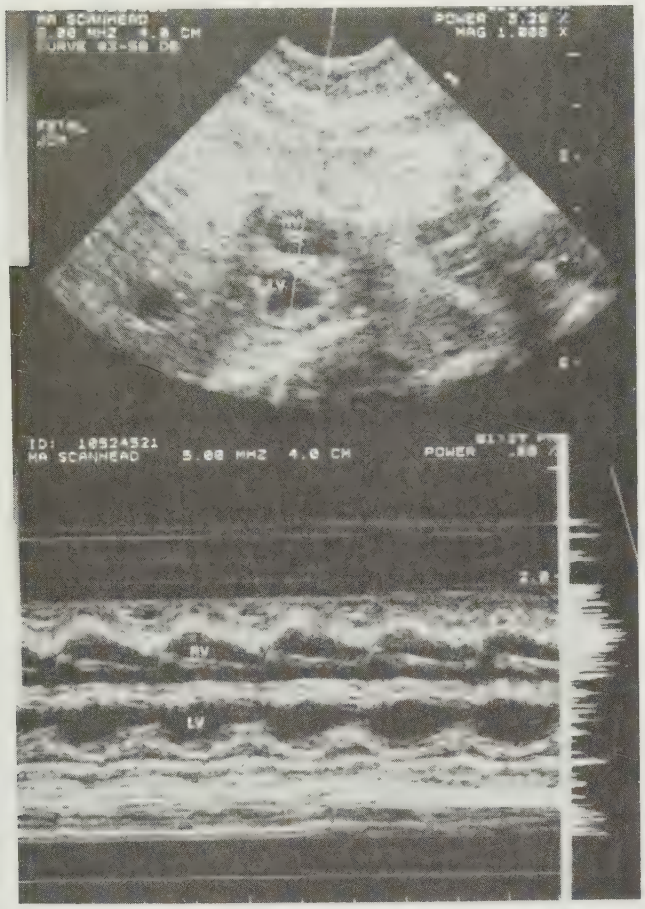

Fig. 48–26. Demonstration of two-dimensionally directed M-mode echocardiogram in a fetus with normal ventricular size and function. The M-line is directed through the right ventricle (RV) and left ventricle (LV) in the short axis at the level of the atrioventricular valves (upper panel). The M-mode echocardiogram (lower panel) demonstrates normal ventricular size and normal right ventricular and left ventricular free wall motion. Note that septal motion is relatively flat in the fetus.

Substantial differences in ventricular geometry may produce greater right ventricular end-diastolic and end-systolic volume and, consequently, greater right ventricular stroke volume. Anzacot[23] described changes in left and right ventricular geometry in the short axis from a left ventricular cross-sectional configuration of a flattened ellipse in the fetus, a circle in older infants, and transitional shapes in newborns. Left ventricular shape in the fetus and newborn was similar to left ventricular shape observed in postnatal patients with congenital heart disease that produces right ventricular pressure or volume overload. Thus although right and left ventricular transverse diameter in the four-chamber view may be equal, differences in three-dimensional ventricular geometry may reflect the dominance of the right ventricle in fetal circulation.

Echocardiographic parameters of ventricular function are load dependent and are therefore of limited use in the assessment of contractile state. The parameters that are employed in postnatal life are primarily ejection phase indices such as the pre-ejection/ejection period ratio, shortening fraction, mean velocity of shortening, and ejection fraction. Although an assessment of systolic time intervals in the human fetus is possible[17,42] by using transabdominal fetal electrocardiograms, these measurements are affected by changing afterload and are technically difficult to obtain. Kleinman and Donnerstein[17] have demonstrated an increasing pre-ejection/ejection period ratio with gestational age. Postextrasystolic potentiation in the human fetus has been demonstrated by using M-mode recordings and assessment of shortening fraction and peak systolic wall velocity. The presence of postextrasystolic potentiation is probably the result of increased preload and as such confirms the presence of a Starling response in the human fetus. Fractional shortening of the right and left ventricles appears to be similar at approximately 32%[19] (standard deviation = 4%) and decreases slightly from 20 weeks to term.[21,43] However, conclusions concerning the contractile state of the fetal myocardium cannot be reached in any given clinical setting because of inability to assess changes in fetal loading conditions. In addition, comparison of left ventricular shortening fraction in the fetus to shortening fraction in the neonate and infant is not possible because of changes in ventricular geometry with birth. Ultimately, right ventricular enlargement, pleural and pericardial effusions, and scalp edema are noted in the fetus with heart failure. However, these changes occur late in the course of fetal heart failure.

Pulsed and Continuous Wave Doppler

As was described above, pulsed Doppler examination of the fetal heart is useful in the diagnosis of fetal arrhythmia and may be used to estimate fetal blood flow, to detect valvular insufficiency, to demonstrate turbulent great vessel flow, and to detect constriction of the fetal ductus arteriosus. The pulsed Doppler examination of the human fetus has been described.[44–48] However, a number of factors add to the difficulty of performing Doppler examination of the fetus. Pulsed and continuous-wave Doppler examination exposes the fetus to higher-intensity ultrasound energy than does either two-dimensional or M-mode imaging. In addition, Doppler sampling often must be performed at a greater depth in the fetus despite the necessity of limiting ultrasound energy output. This may lead to a poor signal-to-noise ratio and to frequency aliasing. In addition, because of variations in fetal position, velocities cannot always be recorded from all four cardiac valves, and optimal angles for pulsed Doppler sampling often cannot be obtained. Angle correction of recorded velocities is necessary if volume flow is to be estimated. Measurements of fetal valve orifice or vessel diameters are frequently obtained at the limits of resolution of two-dimensional imaging and therefore can introduce significant error into the calculation of volume flow. Despite these limitations, pulsed Doppler examination is a useful adjunct to cardiac evaluation of the fetus. Although adverse effects of Doppler examination of the human fetus have not been demonstrated, addition of Doppler to cardiac imaging should not be considered routine. Indications for pulsed Doppler examination include:

1. demonstration of abnormal flow in patients with suspected congenital heart disease,
2. diagnosis of fetal arrhythmia,
3. assessment of cardiac function in the fetus at risk for congestive heart failure.[45]

In addition to using minimum energy output, the pulsed Doppler examination should be performed with the smallest possible sample volume size. In the four-chamber view, Doppler sampling

should be performed at the atrioventricular valve orifice to obtain maximal diastolic atrioventricular valve flow and, in addition, proximal to the valve to detect atrioventricular valve insufficiency. Atrioventricular valve insufficiency is often recognized in the fetus with nonimmune hydrops and heart failure (Fig. 48–27).[49] Atrioventricular valve insufficiency may also be noted in association with congenital heart disease such as Ebstein's anomaly (Fig. 48–28) or atrioventricular canal defects.

Flow velocity can be recorded from the tricuspid or mitral valve in approximately 50 to 60% of fetuses.[47] In contrast to infants and adults, fetal atrioventricular velocity profiles demonstrate dominant A wave (Fig. 48–18). The ratio of the E wave to the A wave increases during gestation.[47] It has been postulated that the A wave dominance in the fetus reflects reduced ventricular compliance and suggests a dependence on atrial systole to ensure adequate ventricular filling.[44–47] When adequate velocity profiles are obtained from both atrioventricular valves, calculated tricuspid flow exceeds mitral flow by approximately 30%.[44]

Doppler sampling in the foramen ovale reveals flow from right to left, which is accentuated with atrial systole. Interrogation of the left ventricular inlet reveals characteristic mitral inflow and left ventricular outflow, which is useful in demonstrating atrioventricular activation sequence (Fig. 48–18). Ascending aortic flow velocities may be obtained from views simulating the apical long-axis view or the suprasternal notch view. Angles obtained from the suprasternal notch view are often suboptimal and exceed 20°. Flow velocities distal to the pulmonary valve may be recorded in modified short-axis views (Fig. 48–29). Doppler interrogation of the ascending aorta and pulmonary artery is useful in detecting significant degrees of semilunar valve stenosis (Fig. 48–30). Aortic or pulmonary velocity can be successfully obtained in approximately 60% of fetuses.[47] When aortic and pulmonary flow are calculated from angle-corrected velocity, pulmonary flow exceeds calculated aortic flow by approximately 30%.[44,47] With fetal growth, increasing atrioventricular and semilunar valve flows occur largely as the result of increasing valve diameter, since velocity and heart rate changes are relatively minimal during gestation and increases in valve diameters are at least twofold.[47,48]

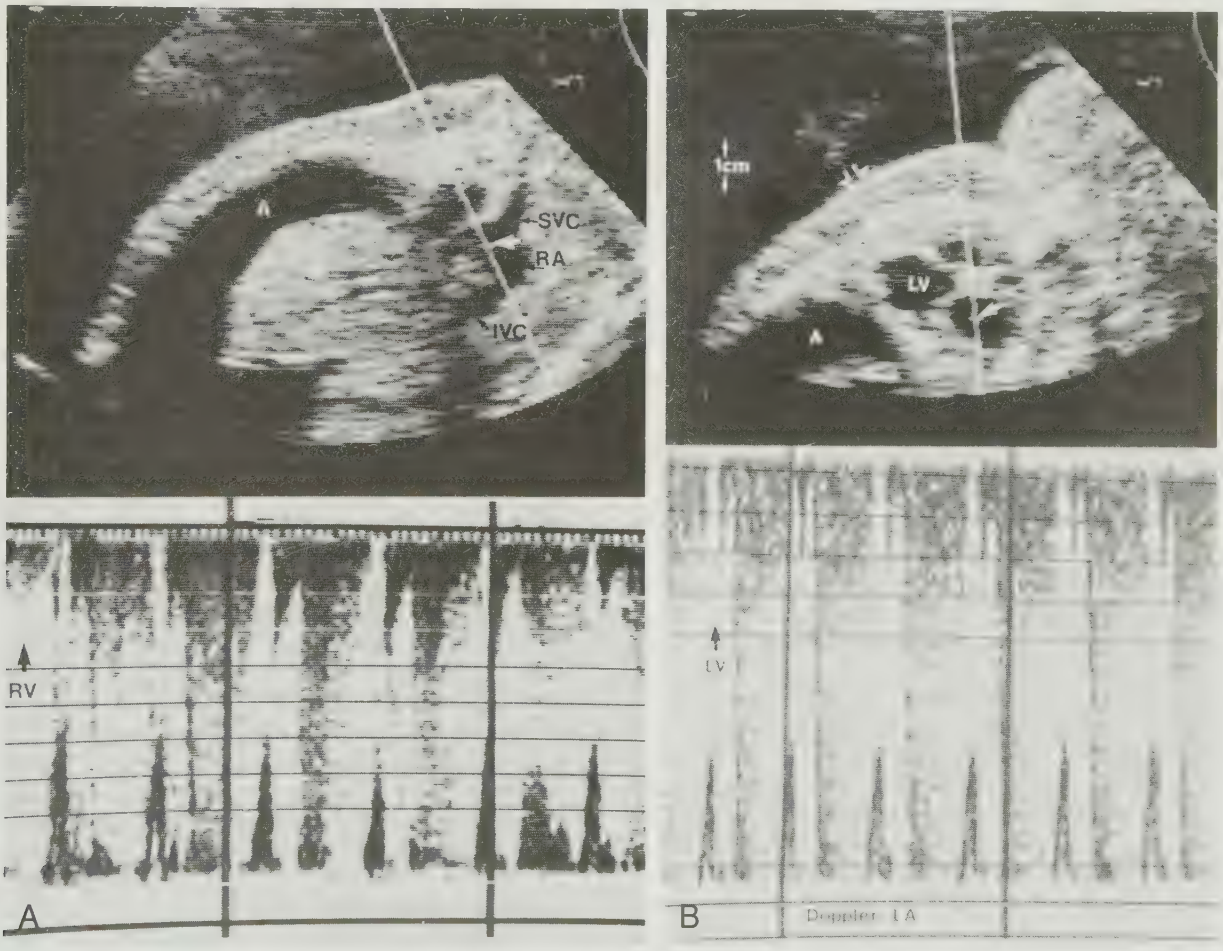

Fig. 48–27. (a) Tricuspid insufficiency detected by pulsed Doppler in a fetus with nonimmune hydrops. In the upper panel, the Doppler sample volume is positioned in the right atrium (RA). The presence of ascites (A) is an indication of fetal hydrops. In the lower panel, the high-velocity jet of tricuspid insufficiency is demonstrated. RV = right ventricle; IVC = inferior vena cava; SVC = superior vena cava. (b) Mitral insufficiency demonstrated by Doppler sampling in the left atrium (LA) in a fetus with nonimmune hydrops (upper panel). The arrow is directed at fetal chest wall edema. The presence of edema and ascites (A) indicates advanced fetal hydrops. In the lower panel, the high-velocity jet of mitral insufficiency is directed from the left ventricle (LV) to left atrium (LA).

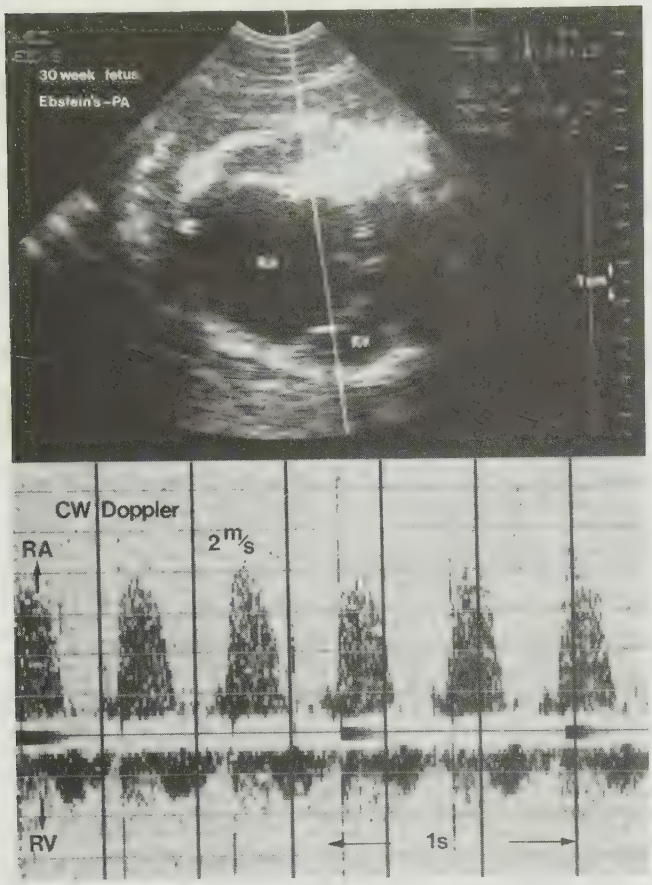

Fig. 48–28. Continuous-wave (CW) Doppler sampling of tricuspid insufficiency in a 30-week fetus with Ebstein's anomaly. The two-dimensional scan (upper panel) is in a transverse plane from posterior to anterior (PA) and demonstrates massive right atrial enlargement with inferior displacement of the tricuspid valve. The line of continuous-wave Doppler sampling is also illustrated in the upper panel. In the lower panel, the jet of tricuspid insufficiency peaks at 2 meters per second (m/s). RA = right atrium; RV = right ventricle; s = second.

Sagittal imaging allows demonstration of the ductus arteriosus in continuity with the descending aorta. Sampling in the ductus arteriosus (Fig. 48–29) generally reveals the highest flow velocities recorded in the fetus. Ductal velocities are higher than either ascending aorta or pulmonary artery velocities, range from 0.6 to 1.2 m/s, and increase with increasing gestational age. Diastolic velocities of 0.1 to 0.2 m/s toward the descending aorta are characteristic of ductal flow. Huhta and associates[50] have recently demonstrated ductal constriction in fetuses exposed to indomethacin in utero. A characteristic pattern of increased peak ductal velocity and exaggerated diastolic runoff toward the descending aorta was demonstrated. This pattern was similar to the velocity profile obtained by continuous-wave Doppler in coarctation of the aorta. Since the greatest portion of cardiac output in the fetus flows through the ductus arteriosus, changes in ductal velocity would reflect either ductal constriction or changes in right ventricular output. Therefore altered ductal flow velocity may be a useful parameter for assessment of right ventricular function and ductal constriction.

In addition to measurement of cardiac and great vessel flow velocity, pulsed and continuous-wave Doppler methods have been applied directly to the measurement of placental blood flow and indirectly to the estimation of placental resistance.[51–68] By using duplex pulsed Doppler echocardiography and continuous-wave Doppler, umbilical artery and vein flow velocities may be measured at the insertion of the umbilical cord on the surface of the fetal abdomen (Fig. 48–31). Umbilical vein flow velocity can also be sampled in the fetal abdomen as the umbilical vein courses toward the liver (Fig. 48–32). Flow in the descending aorta may be sampled at the level of the fetal diaphragm in the sagittal plane with measurement of the angle to flow. Continuous-wave Doppler has also been used with and without two-dimensional imaging to measure umbilical vein, descending aorta, and umbilical artery flow velocities.

The accuracy of calculated placental blood flow using the measurement of velocity of blood flow in the umbilical artery or vein is affected by several factors. First, an accurate measurement of vessel diameter in small fetuses is difficult to obtain within the limits of resolution of two-dimensional ultrasound. In small subjects, a small error in measurement of vessel diameter results in a proportionately large error in calculation of vessel cross-sectional area. The umbilical vein and descending aorta are assumed to be circular in cross section, and phasic changes in vessel cross-sectional area are not taken into account. Second, the calculation of spatial mean velocity of blood flow from spectral velocity wave forms depends on the assumed shape of the spatial velocity profile in the insonated vessel. The velocity profile in the descending aorta is presumed to be parabolic in the fetus, the highest velocity being in the center of the vessel. Third, the angle between the umbilical artery or vein and the ultrasound beam may not be estimated accurately.

With these limitations in mind, it is not surprising that there is considerable variation among individual measurements of fetal blood flow at any gestational age. Nonetheless, some hemodynamic trends can be observed during gestation. In general, umbilical and aortic flows increase with increasing gestational age with a slight reduction in flow in the two weeks prior to term.[52–57,61,62,67] The increase in flow occurs as a result of increasing vessel diameter with umbilical venous mean velocity remaining constant. Mean calculated umbilical vein flow in most studies ranges from 100 to 120 mL/kg/min with descending aorta flow averaging approximately 200 mL/kg/min. Thus the ratio of umbilical flow (or placental flow) to descending aortic flow determined by Doppler in human fetuses is approximately 60%. Increased umbilical flow has been observed in the presence of maternal anemia, maternal hemorrhage, and fetal isoimmune hemolytic disease,[57] with decreasing flow in fetal subjects with imminent asphyxia.[62] Descending aortic mean velocity is also decreased in the presence of maternal hypertension with fetal growth retardation, particularly in the presence of fetal distress.[60] This is both a result of reduced peak velocity and a result of the virtual absence of normal forward diastolic flow velocity.

Forward diastolic flow in the descending aorta and umbilical artery probably results from diastolic runoff to the low-resistance placental circulation. A number of indices of diastolic flow have been developed in an attempt to quantitate changes in placental resistance.[51,58,60,62,63,65,66,68] These include the ratio of maximal systolic to maximal diastolic flow and the pulsatility index ($V_{peak} - V_{min}/V_{mean}$). There is a general trend for the pulsatility index to

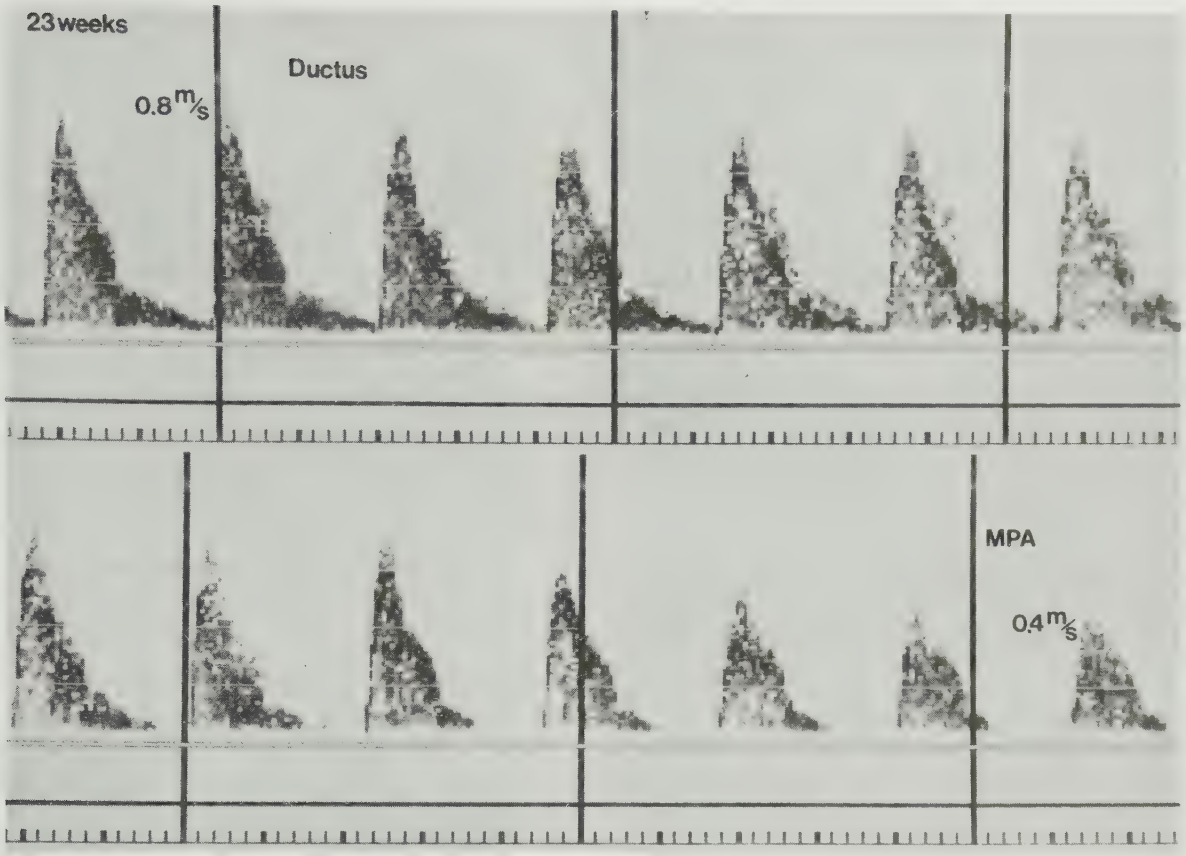

Fig. 48–29. Pulsed Doppler sampling of ductus arteriosus flow and main pulmonary artery (MPA) flow in a 23-week fetus. Ductal peak velocity is 0.8 meter per second (m/s) with continuous diastolic runoff. As the sample volume is withdrawn to the main pulmonary artery, peak velocity decreases and the pattern of continuous diastolic runoff is lost.

decrease with increasing gestational age in some studies,[58] whereas in others there is essentially no change with increasing gestational age.[65,66] In general, as placental resistance increases—for instance, in the fetus with intrauterine growth retardation—diastolic flow is reduced, and the pulsatility index or ratio of systolic to diastolic flow increases.[51,58,60,63,65,68] An increased pulsatility index has been observed in fetal subjects with imminent asphyxia.[62] Diastolic velocity may approach zero, and reversal of flow has been observed in some cases (Fig. 48–33). In contrast, maternal hypertension without growth retardation and isoimmune hemolytic disease do not appear to affect the pulsatility index.[60] The normal pulsatility index is usually less than 2, with some overlap between normal and abnormal subjects in the range from 2 to 3. A pulsatility index greater than 3 is abnormal and may indicate high placental resistance. Although these parameters of placental blood flow and resistance are provocative and provide some insight into fetal hemodynamics, their contribution to the early detection and treatment of the fetus at risk for significant asphyxia remains to be determined.

COLOR DOPPLER FLOW IMAGING

Color Doppler flow imaging may enhance the fetal echocardiographic examination in a number of ways.[69] Because of the lower pulse repetition frequency of color flow systems, energy intensity is less at any given area and therefore is less likely to be harmful to the fetus than conventional pulsed Doppler or continuous-wave Doppler. Poor two-dimensional imaging may be encountered in a number of situations including maternal obesity, polyhydramnios, and advanced fetal gestational age. The addition of color Doppler to the examination may allow differentiation of structures that are not readily identified by two-dimensional echocardiography alone. The use of color Doppler may shorten the duration of conventional Doppler examination by allowing quick recognition of normal and potentially abnormal flow. Identification of pathologic jets, such as tricuspid insufficiency or turbulent jets of semilunar valve stenosis, may allow directed conventional pulsed Doppler examination to the area of interest. In addition, color Doppler may allow identification of direction of flow and improve angle correction of velocities. There are some limitations to the color Doppler examination in the human fetus. The lower pulse repetition frequency of color Doppler, as well as the greater depth of sampling in the fetus, leads to frequency aliasing at lower velocities. Sampling at greater depths with the small volume flows encountered in the fetus may lead to low signal amplitude because of the reduced intensity of backscattered ultrasound. Current color Doppler systems have reduced spatial resolution because of the relatively low carrier frequencies employed and reduced temporal resolution because of the slow frame rates required for color Doppler signal processing. Since Doppler signal amplitude is greatest in the axis

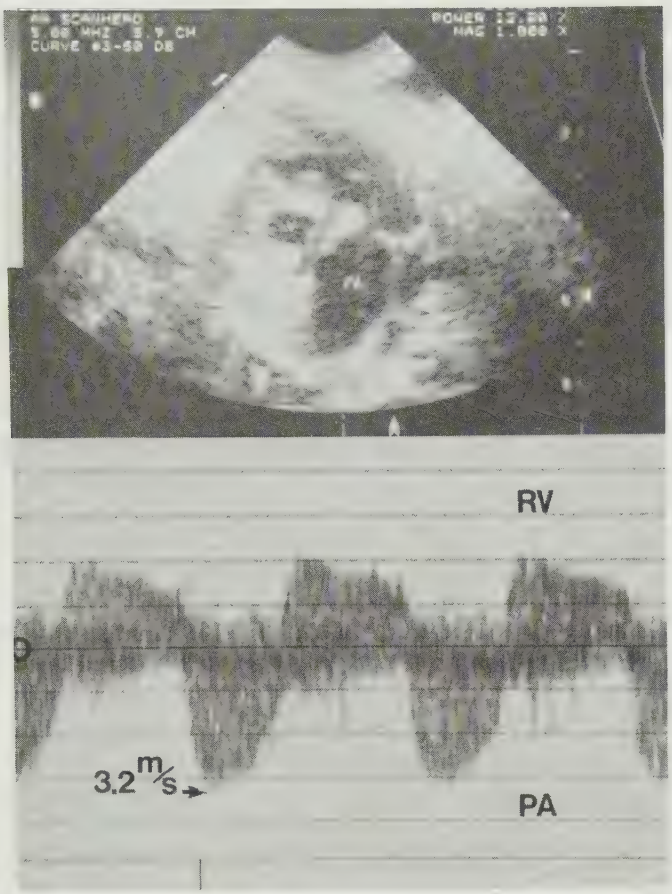

Fig. 48–30. Pulmonary stenosis and insufficiency in a fetus with absent pulmonary valve syndrome. In the upper panel, the arrow is directed at the pulmonary anulus, and massive enlargement of the pulmonary artery (PA) is easily appreciated. The continuous-wave Doppler recording in the lower panel demonstrates pulmonary stenosis with a peak velocity of 3.2 meters per second (m/s) and pulmonary insufficiency with a peak velocity of 2 meters per second. RV = right ventricle; LV = left ventricle.

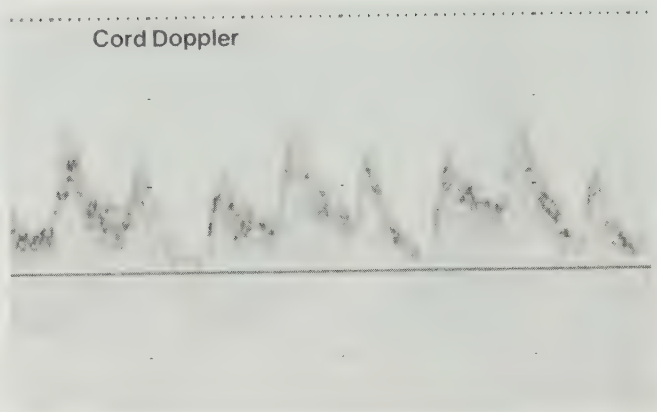

Fig. 48–31. Continuous-wave Doppler recording of umbilical cord flow. The pulsatile "sawtooth" pattern of umbilical arterial flow is upward, directed toward the transducer, and varies with fetal breathing. Note the continuous nature of normal umbilical arterial flow. Umbilical venous flow, which is downward, directed away from the transducer, also varies with fetal breathing but is not pulsatile.

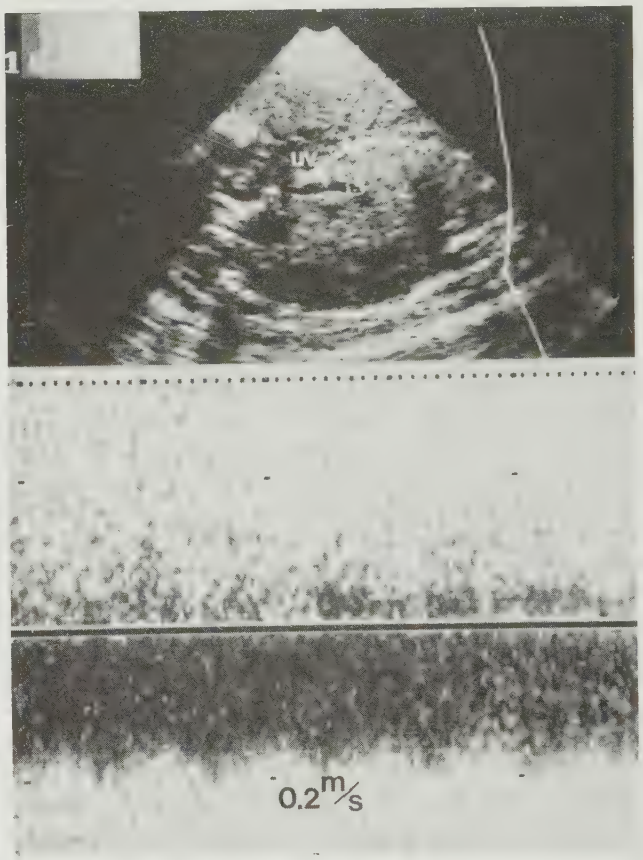

Fig. 48–32. The site of pulsed Doppler sampling of the umbilical vein (UV) as it enters the fetal liver (upper panel). Flow in the umbilical vein (lower panel) is of low peak velocity and demonstrates significant spectral dispersion, reflecting nonlaminar flow conditions.

of flow, the optimal images for color Doppler sampling are often at right angles to the best plane of imaging for two-dimensional echocardiography.

Since standard image orientation is often not obtained in the fetus, the usual color patterns of intracardiac flow are not seen in many cases. The color of the Doppler flow signal depends on the orientation of the heart relative to the scanhead. For instance, in the normal fetus, atrioventricular valve flow is seen as a red jet in diastole when recorded from an apical position in the four-chamber plane. However, atrioventricular valve flow is depicted as blue if the four-chamber view is recorded from base to apex. The blue jet of semilunar valve regurgitation may be seen in the apical four-chamber plane or in a modified long-axis scan from the apex. Enhanced recognition of atrioventricular valve insufficiency may aid in the early diagnosis of congestive heart failure in the fetus and in differentiation of degrees of tricuspid insufficiency associated with progression to fetal hydrops.[49] In the modified long-axis view, great vessel flow demonstrates contrasting colors, pulmonary and ductal flow away from the transducer being

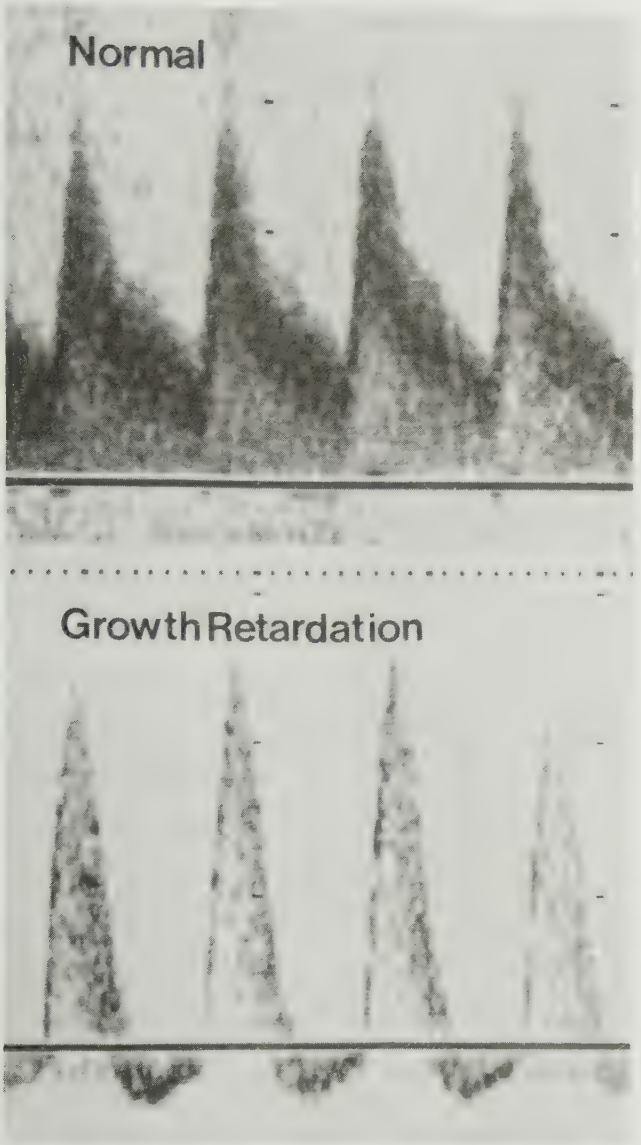

Fig. 48–33. Pulsed Doppler sampling of flow in the umbilical artery. In the upper panel, the typical "sawtooth" pattern of normal umbilical arterial flow is seen with continuous diastolic runoff and relatively high end-diastolic velocity. A markedly abnormal pattern of umbilical arterial flow is seen in the lower panel with flow reversal during diastole. Reduced umbilical arterial diastolic velocities or flow reversal is often detected in the fetus with intrauterine growth retardation or imminent asphyxia.

encoded blue and ascending aortic flow toward the transducer encoded red. Ductal flow may demonstrate aliasing as a result of the relatively high velocity of ductal flow in the fetus. Right-to-left flow across the foramen ovale is usually easily demonstrated in the fetus. Left-to-right flow implies a severe degree of obstruction to inflow at the mitral valve and may suggest the presence of mitral atresia or stenosis. The streaming of inferior vena caval flow to the left atrium and of superior vena caval flow to the right ventricle can be demonstrated in some subjects. The characteristic spiral course of the umbilical vessels with alternating red and blue color is easily demonstrated. With improvements in technology, the contribution of color Doppler flow imaging to cardiac diagnosis in the fetus should continue to increase.

RISKS AND BENEFITS OF FETAL ECHOCARDIOGRAPHY

The potential for damage to the fetus by ultrasonic examination is related to many factors.[70–72] The frequency of ultrasound, commonly from 2 to 10 mHz in echocardiography, is probably a major determinant of adverse tissue effects. The duration of exposure and the pattern of exposure, such as pulsed versus continuous ultrasound, also have a major impact on the amount of ultrasonic energy delivered to fetal tissues. The duration of exposure when using pulsed ultrasound varies with the pulse repetition frequency and the duration of the pulse. Thus the greatest tissue effects at a given carrier frequency would be expected with continuous ultrasound exposure and would be least with low pulse repetition frequencies of sort pulse duration. Tissue effects result from absorbed ultrasound and therefore decrease with increasing distance from the ultrasound source. The amount of energy transmitted is also altered by differences in tissue characteristics between the ultrasound source and the area of potential damage. Biologic mechanisms that come into play under conditions of ultrasound exposure also modify tissue effects. Thus the problem of assessing risk of fetal exposure is very complex and varies greatly depending on choice of instrumentation, fetal and maternal size, presence of edema or altered quantities of amniotic fluid, type of ultrasound examination performed, and duration of examination among other variables.

Ultrasound exposure may damage tissue in a number of ways. As ultrasound energy is absorbed by tissue, heat is generated. The amount of heat generated decreases with increasing depth from the source. However, the degree of local heating that induces damage depends on the temperature threshold for cellular damage and the mechanisms for heat removal at the area of exposure. The ability to remove heat is a function of blood flow and the time between exposures to ultrasound to allow for heat removal. In addition, ultrasound exposure generates or adds to gas bubbles in tissue, called cavitations. The development of cavitations also depends on ultrasound frequency and duration of exposure. Both increasing temperatures and increased gaseous cavitations can lead to cell death.

It should be apparent that there is no simple way to estimate the risk of tissue damage from diagnostic ultrasound. There are threshold intensity levels that appear to be safe to the human fetus even with continuous exposure. Higher threshold intensities are tolerated with pulsed ultrasound. There appears to be little risk with carrier frequencies and pulse repetition frequencies employed for two-dimensional and M-mode echocardiography. However, evaluation of the fetal heart by Doppler echocardiography requires higher-energy exposure than imaging alone because of higher pulse repetition frequencies. The exposure may exceed the current federal guideline of 100 mW/cm^2 spatial peak temporal average. Although it is difficult to estimate exposure, ultrasonic examination should be kept to the minimum time required using the lowest possible energy output, with particular attention to limiting the amount and duration of Doppler examination. Doppler examination should be performed only when clinical indications exist and not as a routine screening method. Continuous-wave Doppler ex-

amination should not be performed when pulsed Doppler examination will yield equivalent information. When repeated examinations are required, Doppler should be performed only when a potentially life-threatening abnormality exists. Direct Doppler sampling should be confined to the heart, great vessels, and umbilical vessels with strict avoidance of the central nervous system, the eyes, and the gonads.

The potential benefits of fetal ultrasound, except as noted above, greatly outweigh the risks. It is difficult to measure the positive physical and psychologic effects of excluding serious fetal congenital heart disease with a prior history of major congenital heart defects in a sibling or parent. When significant structural defects are detected, the physician's responsibility is to inform the parents of the natural history of the defect in the fetus and in the child with a review of the available options. Unfortunately, the natural history of some defects in utero is not clear. The ultimate severity of a defect detected in utero can be overestimated or underestimated. This is particularly likely to occur when a combination of defects is present, such as atrioventricular canal and tetralogy of Fallot. In addition, the medical and surgical treatment for many forms of congenital heart disease is evolving. Likewise, the current approach to in utero treatment of the fetus is evolving and holds promise for developments that will directly affect treatment of the infant with congenital heart disease. If the fetus with a significant defect survives pregnancy, delivery at a medical center that is equipped to care for critically ill neonates can be planned, and preparations can be made for early intervention by a pediatric cardiologist. The decision to terminate pregnancy depends on all of the above considerations and is ultimately an ethical decision calling for an assessment of the potential quality of life and longevity of the affected human fetus.[16]

The benefits of accurate diagnosis of fetal arrhythmia are clear and include (1) the ability to institute specific therapy in utero, (2) the avoidance of unnecessary cesarean section, and (3) the ability to plan for delivery at a medical center that is equipped to manage neonates with abnormalities of heart rhythm. Recognition of heart failure in utero allows treatment that may prolong fetal survival until delivery can be accomplished. Evolving methods of evaluating cardiac function may lead to early recognition of congestive heart failure in utero. Abnormal patterns of descending aorta, umbilical artery, or umbilical venous flow imply reduced placental blood flow and increasing placental resistance and, in some instances, precede changes in other indices of placental insufficiency or impending fetal asphyxia. Recognition of these abnormal patterns promises to allow early diagnosis of fetal distress and may be useful in identifying the fetus at risk for asphyxia.

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CHAPTER 49

Exercise Testing

Frank M Galioto, Jr

Exercise testing has become increasingly important in pediatric cardiology centers.[1–4] Such testing is most recognized as useful in detecting cardiac abnormalities that are silent at rest and become manifest only with physiologic stress. Yet in combination with other modalities, exercise testing can lead to a more precise definition of the extent of heart disease in a child or adolescent with known cardiac abnormalities. Stress testing may be an effective screening tool for children in the appropriate setting and is the major tool for assessing the physiologic responses to exercise in normal children.[5,6]

Monitored exercise testing is useful for an objective assessment of symptomatology that the patient senses during physical activity. Since physical activity is an important part of each child's life, it is common that various forms of heart disease may become manifest during these periods of activity. It is therefore important to be able to reproduce the stress of exercise in the controlled, safe environment of the exercise laboratory to ascertain the exact cause of the symptoms perceived by the patient.

The extent to which the exercise test discloses abnormalities in cardiac function is directly related to the number of parameters assessed during exercise. To assess an impairment of cardiac output in a patient who has had surgery for congenital heart disease, cardiac output should be measured during exercise. Indirect measures of cardiac output, for example, the measurement of a ventilatory parameter such as oxygen consumption, are less precise and may lead to erroneous conclusions.[7]

INDICATIONS

The usefulness of exercise testing as a screening tool is subject to much debate. The results of mass screening should be judged according to the specificity and sensitivity of the tool used. If one measures the exercise capabilities of a group of seemingly normal children, there will be a range of "normal" findings. In normal children, the most common "diagnosis" will be that of exercise intolerance due to a lack of conditioning. These children are not abnormal, and the data should be interpreted only in reference to a range of normal responses. If one is interested in screening individuals for hypertrophic cardiomyopathy, which is a common cause of sudden death during exercise in young individuals, the most useful tool should be echocardiography and not stress testing.[8] On the other hand, if one is most interested in exercise-induced ventricular tachycardia, then there is no substitute for exercise testing. Similarly, the exercise test is useful for that small group of individuals with congenital abnormalities of the coronary arteries that predispose them to ischemia.[9] In these individuals, an exercise test will produce changes on the exercise electrocardiogram and will yield diagnostic information. However, for the overwhelming majority of patients, the exercise test will be a screening test for conditioning and not for congenital heart disease.[10,11]

Exercise testing is used most often in evaluating exercise-induced symptoms such as chest pain or syncope when heart disease is considered part of the differential diagnosis. Studies in which the test has been diagnostic include those for the diagnoses of exercise-induced asthma, coronary artery abnormalities, and exercise-induced arrhythmia. Exercise testing is considered especially valuable in the assessment of patients with known problems such as those following repair of structural congenital heart dis-

ease, with valvar heart disease that has not yet been repaired, with systemic hypertension, and with exercise-related arrhythmia.

Each pediatric exercise laboratory has a slightly different methodology, depending upon the personnel involved and the equipment selected for use. Because of these differences, each exercise laboratory must develop its own series of normal values for children and adolescents of different ages. The results obtained in the testing of children with abnormalities should be compared against the results obtained from normal subjects in one's own laboratory rather than to a series of patients in the literature. Often the testing modalities and the patient selection from the literature are quite different from the equipment in and population served by an individual exercise laboratory; thus it is inappropriate to use published norms.

METHODOLOGY

Exercise Inducers: Bicycle Versus Treadmill

The initial key selection of equipment in establishing the pediatric exercise laboratory is that of the exercise inducer. Generally, there are two types of exercise inducers: the motorized treadmill and the bicycle ergometer.[12] Each has its advantages and disadvantages. The treadmill is larger, is somewhat more costly, and does not allow for a precise determination of the amount of work induced. It is, however, more easily adaptable to patients of various sizes, and children as young as 2 years of age have successfully completed treadmill exercise-testing protocols. Testing of very young subjects is usually not possible with a mechanically or electrically braked bicycle ergometer. The treadmill induces slightly more work in terms of oxygen consumption than the bicycle ergometer because a greater number of muscle groups are active during running than during pedaling the ergometer. The use of the treadmill makes the measurement of blood pressure more difficult because of the motion of the arm during running.

A bicycle ergometer is often less expensive than a treadmill and occupies a smaller area of the exercise laboratory than the treadmill. The bicycle can be calibrated precisely, and therefore the exact number of watts accomplished by the subject can be precisely measured.[13] The ergometer is also more useful for individuals who cannot use their legs effectively for exercise. In these cases, the device can be arranged into an arm crank apparatus that will allow for exercise testing. The major drawback to the commercially available bicycle ergometers is that these machines often call for a starting cranking power greater than that achievable by many small children. This is a special problem in laboratories in which a large segment of those to be studied are under 8 years of age. This problem is most acute in laboratories where there are no mechanically braked bicycles but only an electrically braked apparatus. The electrically braked bicycles are all designed for adults and have high initial power levels that are often not achievable by small children. This problem can be overcome by starting the crank of the ergometer with the aid of an assistant and having the patient only maintain appropriate cranking speed, but this maneuver alters the work calculations.

The bicycle ergometer has found most favor in Europe, while the treadmill is used more extensively in the United States. The European investigators[13] have spent considerable effort standardizing the ergometer. Their studies have led to a crank length of 33.3 cm with a crank axis height from the floor of between 80 and 120 cm. The flywheel of the ergometer has been standardized to 100 kg. For adult usage, the work calculations call for different numbers of revolutions per minute per unit of resistance. Because these settings are beyond the capability of most children, any pediatric laboratory that uses bicycle ergometers or arm crank devices should establish its own standards. Modifications to crank arm length are mandatory, given the range of sizes of children's legs.

Bicycle ergometry protocols usually call for starting power levels of 25 W and increments of 5, 10, or 25 W. The more fit adolescent may start at levels of 50 W, but the small child should be started at lower levels if the ergometer can be set below 25 W. The most commonly used protocol in Europe was described by Sjostran and calls for three stages with work intervals of 6 min each. In the United States, James and co-workers have described a 3-min incremental protocol in which the work load is based on the subject's body surface area.[14] (See Table 49–1.)

It is important that the ergometer be calibrated frequently for accuracy. Calibration is relatively simple in the mechanically braked device. An inexpensive calibration set is usually made available at the time of purchase of the ergometer. Calibrating an electrically braked system is much more difficult and often requires a service call by the manufacturer's representative to ensure that the device remains accurate.

Table 49–1. Fixed Continuous Bicycle Protocol with Three Exercise Programs

Exercise Level (3 min spent at each level)	*I (BSA < 1 m²) Workloads (kg-m/min)*	*II (BSA = 1–1.9 m²) Workloads (kg-m/min)*	*III (BSA > 1.2 m²) Workloads (kg-m/min)*	*Cumulative Time (min)*
1	200	200	200	3
2	300	400	500	6
3	500	600	800	9
4	600	700	1000	12
5	700	800	1200	15
6	800	900	1400	18
7	900	1000	1600	21
8	1000	1100	1800	24
9	1100	1200	2000	27
10	1200	1300	2200	30

BSA = body surface area in square meters.

From James, F.W., et al.: Responses of normal children and young adults to controlled bicycle exercise. Circulation, *61*:902–912, 1980.

Table 49–2. Bruce Protocol

Stage	Duration (min)	Speed (mph)	Grade (%)	Mets
Rest/recovery		0.0	0.0	
1	3:00	1.7	10.0	4.5
2	3:00	2.5	12.0	7.0
3	3:00	3.4	14.0	10.0
4	3:00	4.2	16.0	12.9
5	3:00	5.0	18.0	15.0
6	3:00	5.5	20.0	16.9
7	3:00	6.0	22.0	19.1

From Bruce, R.A., and McDonough, J.R.: Stress testing in screening for cardiovascular disease. Bull. N.Y. Acad. Med., *45*:1288–1305, 1969.

The treadmill does not have a similar calibration because the number of steps that a child takes during running exercise to keep up to the speed of the treadmill varies from one individual to the next. This variability makes much more difficult an assessment of the amount of work done. However, standard protocols have been developed by a series of investigators. The most commonly used protocol is that described by Bruce and McDonough.[15] (See Table 49–2.) The treadmill speed and incline are increased every 3 min with the Bruce protocol. The initial speed is set at 1.76 mph and the grade at 10%. After 3 min, the speed is increased to 2.5 mph and the incline to 12%. After another 3 min, the speed is further increased to 3.4 mph and the grade to 14%. In the fourth stage, after 9 min have elapsed, the speed is increased to 4.2 mph and the grade to 16%.

In the exercise laboratory at Children's Hospital National Medical Center, it has been found that most children cannot exercise consistently above 3.4 mph because of the number of strides required. Therefore the Bruce protocol has been modified to be more suitable for the child. The speed of the treadmill is maintained at 3.4 mph past the third stage, and only the grade is increased. (See Table 49–3.)

Other commonly used protocols for the treadmill are those designed by Balke[16] and Astrand.[12] Astrand's method calls for a stepwise increase in grade while keeping the speed constant. The speed is determined by the subject's ability to run and ranges between 5 and 8.5 mph. In Balke's protocol, a constant speed of 3.3 mph is used, the grade increasing to a maximum of 22% after 22 min. It has been found that the Balke protocol allows for the longest test duration, while the Bruce protocol allows for a shorter test but with a slightly higher maximal oxygen consumption. It is clear from this wide range of results that individual children will respond differently to various protocols. In the pediatric laboratory with a treadmill, the physicians should become proficient in applying just one protocol, and that protocol should be used consistently to allow for uniform comparison between subjects. There may have to be modifications for extremely small children or those who are especially unfit to allow for a long enough exercise test to make various physiologic measurements, but these modifications should be kept to a minimum, since they will produce results that will be difficult to interpret.

Table 49–3. Modified Bruce Protocol for Young Children

Stage	Duration (min)	Speed (mph)	Grade (%)	Mets
Rest/recovery		0.0	0.0	
1	3:00	1.7	0.0	2.3
2	3:00	1.7	5.0	3.5
3	3:00	1.7	10.0	4.5
4	3:00	2.5	12.0	7.0
5	3:00	3.4	14.0	10.1
6	3:00	3.4	16.0	12.9
7	3:00	3.4	18.0	15.0
8	3:00	3.4	20.0	16.9
9	3:00	3.4	22.0	19.1

Electrocardiography

Electrocardiographic monitoring is mandatory during all exercise tests.[17] The patient should have electrodes firmly fastened to his skin in the standard pattern to allow for the recording of all of the leads of the standard electrocardiogram. It should be possible to switch the monitor from one lead to another so that any electrical plane of interest can be viewed. For constant monitoring during the study, three leads from the three orthogonal vector planes should be selected. It most useful to monitor leads I, aV_F, and V_5. It is often advisable to monitor an anterior chest lead in patients who have had right ventricular surgery or are suspected of having right ventricular dysfunction. In these children, V_1 or V_2 is substituted for V_5. At each stage of exercise, a complete electrocardiogram should be recorded at 25 mm/s speed. During the remainder of the exercise test, we have found it extremely helpful to record the three leads being observed on the oscilloscope at a slow paper speed of 5 mm/s. In this way, if an arrhythmia is noticed during the test, the arrhythmia can be easily identified following the completion of the study during the interpretation phase.

A comprehensive resuscitation cart should be present in the exercise laboratory and checked regularly to make sure that all drugs are in date and all apparatus including a defibrillator is functioning without problem. All personnel present during exercise testing must be certified in cardiopulmonary resuscitation and proficient in the techniques of advanced life support.

Blood Pressure

The measurement of blood pressure during exercise is vital, but it is the parameter most recorded in error in children during exercise testing, especially when a treadmill is used.[18–20] If the major purpose of an exercise test is the evaluation of blood pressure in a subject thought to be hypertensive, it is better for that individual to have his exercise test on a bicycle ergometer until more accurate equipment becomes available for assessment of blood pressure during running.

The most commonly used blood pressure device is still the mercury sphygmomanometer and stethoscope. The Korotkoff sounds are auscultated, and the resultant values are recorded manually. Several other methods are available. Doppler detection is theoretically useful, since it does not depend upon the amount of blood flow through the arm for determination of the systolic and diastolic pressures. However, Doppler measurement is subject to a large amount of artifact during any arm movement. Because of this problem with motion artifact, Doppler devices have generally not been used in the clinical exercise laboratory.

The oscillometric method of blood pressure measurement has found favor in some manufacturers' products, but a number of

investigators have shown that the movement of the muscles in the arm causes considerable artifact, and this method has also fallen into disuse.

The most promising method is the automated blood pressure device with a sensitive Korotkoff sound microphone and automated sphygmomanometer. The difficulty with this method is that the reduction of the various sound artifacts in the same frequency and amplitude as the Korotkoff sounds often distorts the Korotkoff sounds themselves. However, a series of new prototypes are being developed with programmable acoustic filters so that the Korotkoff sounds may be better detected and extraneous signals reduced.

Respiratory Gas Exchange

The measurement of gas exchange as oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (V_E) during exercise has been used by many investigators as a gauge of the total effort required by the cardiovascular system.[21,22] Maximal oxygen uptake was the first physiologic parameter measured. Work by Astrand and Rodahl[12] has shown that there is a stable relationship between oxygen uptake and increasing work performed during the aerobic phase of exercise with an eventual plateau in oxygen uptake. The point at which rising oxygen consumption changes to a plateau is called the "anaerobic threshold."[23,24] Some workers have used this point as a marker for conditioning. Its applicability in congenital heart disease has not been thoroughly investigated.

The classic method for measurement of oxygen uptake calls for the use of the Douglas bag.[12] The subject inspires room air, and all gases expired during a given period of time during exercise are collected in a container. The gas is analyzed after the test for oxygen content and volume, and the oxygen consumption for that period is calculated. The use of oxygen uptake measurement has been limited in children because of the difficulty in having the child cooperate enough to create a mouthpiece seal for a prolonged period of time during the collection of expired gases to ensure accuracy of the calculations.

The problem of cooperation has been overcome by the use of the respiratory spectrometer and pneumotachygraph, which reduces the time for collection to a single breath. In this method[25] (Fig. 49–1), the patient inspires room air, and all of the expired gases are vented via a one-way valve through a pneumotachygraph in which the capillary portion of a respiratory mass spectrometer is placed. From the pneumotachygraph, one can detect the volume of each expiration, and the respiratory mass spectrometer gives accurate determination of the amount of expired oxygen and carbon dioxide. From these data, it is possible to calculate oxygen consumption, carbon dioxide production, and minute ventilation on a breath-by-breath basis. This technique is made practical in the clinical setting with the use of an on-line microcomputer to manage the data collection, the various calculations required, and the display of the result in real time.

Whereas the basic exercise test requires only an exercise inducer, electrocardiographic monitor, and blood pressure device, most comprehensive pediatric centers where exercise is being studied in a research effort are routinely measuring oxygen consumption, carbon dioxide production, and minute ventilation. The use of these parameters produces a measure of energy expended, rather than a measure of work performed. The most useful and best-understood measure of effort is that of oxygen consumption.[26,27]

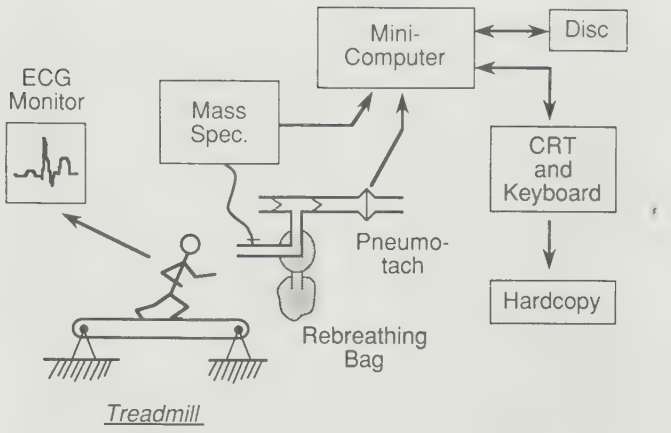

Fig. 49–1. Schematic drawing of the automated exercise laboratory. The patient breathes through the mouthpiece, which is connected to a pneumotachygraph in which the capillary of the respiratory mass spectrometer is placed. The data acquisition and analysis are managed by the on-line computer, which can display the results in real time on the CRT and print them on the hard-copy device.

Obviously, oxygen is needed for muscular work in the locomotion system, for cardiac work, and for the work of respiration in addition to the baseline metabolic processes. These oxygen consumption measurements are those of total oxygen uptake and do not reflect an accurate percentage required by the heart or the musculoskeletal system. For pediatric work, it is important to understand that the limiting aspect for exercise is the amount of oxygen that can be delivered to the tissues of the musculoskeletal system. With the treadmill, the highest amount of oxygen is consumed, since running uses more muscle groups than pedaling the bicycle ergometer.

Maximum oxygen uptake is governed by the ability of the heart to deliver blood to the tissues. Patients with reduced stroke volume and/or heart rate cannot perform as much work as those with normal responses. Similarly, patients with increased peripheral resistance are not able to work to the same level of maximum oxygen uptake.

The practical importance of measuring oxygen consumption is that it is directly related to the performance of the individual. It is well known that the highly trained athlete can achieve much higher oxygen consumption levels than the untrained individual, demonstrating the ability of the isolated measure of oxygen consumption to predict performance. It is important to remember, however, that the maximum oxygen uptake per unit of body weight is greater in a child of 10 years than in an adult for the same amount of work performed.[12] The child is therefore considered a less efficient athlete, since he requires more oxygen to perform the same amount of work.

The use of the carbon dioxide production and minute ventilation allows for better detection of the metabolic "switch" from aerobic to anaerobic mechanisms, the anaerobic threshold.[28] It is assumed that above this level of effort, additional work is being accomplished by the use of nonoxygen-requiring metabolic pathways. Obviously, oxygen is still consumed at a high level, but additional work performed is being done through the use of anaerobic pathways. This threshold is a reflection of the degree of training, since

it has been noted to be higher in the trained athlete and much lower in the less efficient and more sedentary individual.

Cardiac Output

Cardiac output is usually considered to be linearly related to oxygen consumption during submaximal work. Cardiac output at maximal oxygen uptake is less than would be predicted from a linear extrapolation of the cardiac output versus oxygen consumption line.[29] Various investigators have found that children have a low cardiac output in relation to oxygen consumption.[12] In studies in congenital heart disease, it is becoming increasingly apparent that the measurement of cardiac output may be key to the understanding of various exercise responses.

The measurement of cardiac output during exercise is much more difficult than the measurement of other metabolic parameters. The traditional way of measuring cardiac output in cardiovascular practice is in the cardiac catheterization laboratory and utilizes the Fick method. This methodology is unsuitable to the exercise laboratory because of the use of invasive catheters centrally located in the heart during a period of vigorous work and the associated risks of arrhythmia and bleeding. Various noninvasive measures have been developed to meet this need. These methods include the measurement of cardiac output by carbon dioxide rebreathing and by acetylene rebreathing.

The carbon dioxide rebreathing method applies the Fick principle to the exchange of carbon dioxide.[30] It requires the attainment of a steady production of carbon dioxide and requires also the measurement of an arterial sample for carbon dioxide. This can be done by an arterialized capillary blood specimen and the measurement of expired CO_2 for a mixed venous sample. The mixed venous CO_2 sample is obtained by rebreathing from a bag usually containing 5 to 10% carbon dioxide. This requires the subject to be cooperative and willing to withstand some of the discomfort associated with a slightly increased partial pressure of carbon dioxide in the blood. The method has been criticized because the required steady state condition is rarely achieved during exercise. Carbon dioxide is not a physiologically inert gas, and as a result, any increased production because of more work during the period of measurement may lead to an overestimate of cardiac output. Because of these problems, the method is not generally used.

The acetylene rebreathing method for cardiac output measurement is finding increasing use.[31–33,34] The method calls for a closed system of rebreathing achieved with a mouthpiece and noseclip and a prefilled rebreathing bag. The bag is prefilled with known concentrations of helium and acetylene, the balance being oxygen. The helium is used as a marker of uniform distribution of gases, since it is not diffusible across the alveolar–capillary interface, and to ensure that there are no leaks in the system.

With the initiation of breathing from the bag, the helium concentration falls as part of the gas passes into the lungs. On subsequent breaths, helium equilibrates its concentration between the air spaces of the subject's lungs and the bag. At this point, it is assumed that there has been uniform distribution of the gaseous material between the test bag and the subject's lungs. Simultaneous measurement of the acetylene concentration is also made by the mass spectrometer. The acetylene concentration falls with the first breath as acetylene passes into the lungs. Because it is freely soluble in lung tissue and its diffusion is readily accomplished across the alveolar–capillary interface, any disappearance of acetylene from the closed system after the helium achieves equilibrium between the lung and the closed bag indicates that the acetylene is leaving the lung system in the pulmonary blood flow. This rate of disappearance following equilibrium of the helium signal is analogous to the pulmonary capillary blood flow, which is a measure of the cardiac output.

It is important to emphasize that the acetylene rebreathing method will not measure total cardiac output but rather only the amount of blood that (1) reaches the lungs, (2) contacts the alveolar–capillary interface to absorb acetylene, and (3) then leaves the lung. This portion of the cardiac output is referred to as the effective cardiac output (Q_{EP}). If there are right-to-left shunts so that a considerable amount of blood does not reach the alveolar-capillary interface, this portion of the total pulmonary blood flow cannot be detected. Similarly, if there is early recirculation of blood saturated with acetylene as in a left-to-right shunt, the effective pulmonary blood flow measurement by acetylene cannot be accurately measured. It has been shown that the measure of cardiac output by the acetylene method is about 95% of the total pulmonary blood flow in the absence of anatomic shunts (when done simultaneously with Fick measures of pulmonary blood flow in the cardiac catheterization laboratory). Since there is an 18 to 22-s period before recirculation of the gas dissolved in the blood, all measures must be made during this period. Acetylene is tasteless and, in the concentrations used in this type of testing, not flammable. Use of this method is allowing researchers to learn more about cardiac output function during exercise in a variety of pathologic states.

Other Studies During Exercise

Radionuclide angiography[35,36] has been used to assess ventricular function during exercise in many centers. It permits assessment of wall motion of the left ventricle and allows for accurate measurement of ejection fraction. Measurements of right ventricular function are less precise at present. Cardiac output also may be measured by this technique. In children, the major drawbacks to the technique are the total body radiation exposure and the difficulty in keeping the position of the patient's chest constant in relation to the face of the scintigraphy counter for the time required to make enough counts to assure accurate calculations.

The use of echocardiographic and Doppler equipment during exercise is currently under investigation in a number of laboratories.[37,38] Echocardiographic assessment of ventricular performance has been found to be useful in selected individuals with conditions that adversely affect myocardial contractility. The technical problems are those associated with artifact generation because of motion of the transducer against the chest wall and inability to visualize the same area of the heart with each stage of exercise. Because of these problems, many investigators have been using supine exercise with the subject using a bicycle ergometer suspended overhead. This position does not allow for maximal exercise, but in selected individuals this technique has yielded valuable information.

The use of pulsed and continuous-wave Doppler during exercise is undergoing development. The Doppler transducer must be held exactly in the axis of the aortic or pulmonary root during exercise in order to measure velocity accurately. If this position is not achieved, the method is inherently inaccurate. A number of investigators are designing equipment and transducers that will allow

for this measurement; in time, Doppler assessment of cardiac output during exercise may prove to be useful.

Another study that currently has only a research interest is that of pulmonary diffusion during exercise.[39] The pulmonary diffusing capacity is a measure of the gas exchange across the alveolar–capillary interface per unit of pressure. It has been found that athletes with a larger diffusing capacity seem to perform better than their teammates with less diffusing capacity. Physical training does lead to an increase in the maximal diffusing capacity. The role of this measure in patients who have had large left-to-right shunts or cyanotic congenital heart disease remains to be elucidated.

In summary, the simple or basic exercise test should include the use of an exercise inducer, either a treadmill or a bicycle ergometer, electrocardiographic monitoring equipment, and appropriate recording and blood pressure measurement equipment. In a more sophisticated study, oxygen consumption, carbon dioxide production, and minute ventilation are measured in addition to the other parameters. These measurements are usually made at rest, during midexercise, and at peak exercise. If possible, measurements should be made at each stage of exercise. Finally, the most elaborate exercise test calls for the addition of cardiac output measurement. Currently, the use of the cardiac output equipment is not needed for most clinical laboratories and should be reserved for institutions that are conducting research on exercise in children.

CONDUCT OF THE EXERCISE TEST

In the Exercise Laboratory at the Children's Hospital National Medical Center, the usual routine calls for the patient with a parent to be brought to the exercise-testing laboratory. Upon arrival, the exercise technologist reconfirms the height and weight of the patient, as well as judging his psychological maturity and willingness to exercise. Special attention should be given to the very young child, who will need to be encouraged in an age-appropriate manner to exercise to his maximum capability. Parents are cautioned not to overprotect the child. Electrocardiographic electrodes are placed in the usual positions for monitoring during exercise, and leads are attached. All of the electrode and lead apparatus is then covered with a tightly fitting mesh shirt to reduce motion artifact from the leads during exercise (Fig. 49–2). A baseline electrocardiogram is measured with the patient standing on the treadmill and is assessed for rhythm, heart rate, and morphologic features. The baseline parameters for ST segment, QT interval, QRS duration, and PR interval are detemined. A sphygmomanometer or automated blood pressure device is attached to the arm, and the patient is instructed in the operation of the treadmill. The child is shown that the treadmill will increase in speed and in grade and is told that this will take place at various points during the exercise study, and that a maximal effort is expected. The patient is taught how to hold the mouthpiece tight in the mouth. Then baseline measures of oxygen consumption, carbon dioxide production, minute ventilation, and cardiac output are obtained with the output measured by the acetylene rebreathing method (Fig. 49–3). The modified Bruce protocol is usually selected, and when the physician in attendance feels it is appropriate to begin, the test is started. During each phase of exercise, the patient is carefully observed, asked to comment on how he feels, and instructed to report any sensations of chest pain or dizziness. If such events are

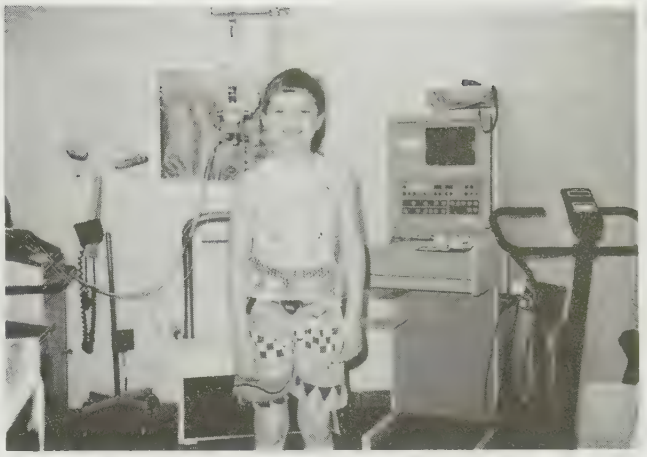

Fig. 49–2. Photograph of a patient on the treadmill illustrating the electrocardiographic electrode placement with the leads held in place by a mesh shirt to reduce motion artifact.

reported and yet there are no signs of any electrocardiographic changes or blood pressure variability, the physician may allow the test to continue. In especially anxious and small children who are not used to sustained exercise, there are commonly complaints of leg fatigue. The patient is encouraged to exercise through these levels of discomfort as long as all other parameters are stable.

If on-line oxygen consumption measures are available, the patient is encouraged to exercise until he is well in the normal range for maximal oxygen consumption for the laboratory. If those parameters are not being measured, the patient is encouraged to exercise to his maximum voluntary effort. A simple way to detect maximal effort is to ask the patient to respond to simple questions. If he is clearly able to take time to speak, then more exercise can be performed. If the child is so engaged with effort that he is unable to speak clearly, this is interpreted as a maximal effort. Cardiac output is measured at what is judged to be midexercise and at the point of maximal exercise.

When it has been determined that the patient can do no more

Fig. 49–3. Photograph of a patient on the treadmill with his mouth tightly around the mouthpiece. For measurement of cardiac output by acetylene rebreathing, breathing is diverted via the valving device into the prefilled bags (white) for 20 seconds.

Table 49–4. Normal Exercise Data in Girls 8 to 12 Years in Age*

	Resting	*Mid Exercise*	*Maximal Exercise*
Heart rate/minute	102.6 ± 16.5 (n=28)	155.6 ± 14.1 (n=28)	194.3 ± 11.7) (n=28)
Blood pressure (mmHg) Systolic	105.4 ± 9.50 (n=28)	120.6 ± 13.3 (n=25)	135.6 ± 13.5 (n=20)
Diastolic	73.0 ± 6.40 (n=26)	74.1 ± 9.90 (n=25)	71.3 ± 10.7 (n=17)
Oxygen consumption (L/min)	0.437 ± 0.23 (n=28)	1.00 ± 0.22 (n=28)	1.29 ± 0.26 (n=26)
Carbon dioxide production (L/min)	0.377 ± 0.18 (n=28)	0.902 ± 0.22 (n=27)	1.28 ± 0.27 (n=26)
Minute ventilation, expiratory (L/min)	12.7 ± 5.05 (n=28)	25.4 ± 6.83 (n=28)	38.9 ± 10.8 (n=26)
Effective pulmonary blood flow, C2H2 (L/min)	3.29 ± 1.32 (n=26)	6.04 ± 1.45 (n=25)	7.87 ± 1.83 (n=22)

*Twenty-eight girls were tested. The average was 10.55 ± 1.00 years; the average weight was 38.64 ± 9.98 kg; and the average standing height was 124.74 ± 9.18 cm.

exercise, the study is terminated by slowing the treatmill gradually and decreasing the grade. Exercise is never stopped abruptly. To avoid peripheral venous pooling and syncope, a recovery period with a slow walk is required for at least 2 min before the patient is allowed to sit. Blood pressure is measured at 1-min intervals during the recovery period, and the electrocardiogram is monitored to observe for signs of arrhythmia or ischemia. The patient is not detached from any of the electrocardiographic or blood pressure apparatus for at least 5 min, or until he has reached within 20% of baseline levels of heart rate and blood pressure.

The criteria for ending an exercise test should be determined before the test is begun. The physician in charge should be familiar with all aspects of the patient's history, diagnosis, and indications for the study. There are certain criteria for premaximal termination that should always be observed. The onset of ventricular tachycardia, defined as three or more consecutive premature beats, should be reason to terminate the test. Exercise-induced hypotension when the systolic blood pressure falls 10 mm Hg or more with an increasing load is another predictor of falling cardiac output. Patients receiving beta-blockers may have an early plateau of heart rate and blood pressure, but even these patients should not have a 10 mm Hg fall in systolic blood pressure. ST-T wave segment depression of 2 mm or more below baseline is caused by ischemia. If these changes are progressive and certainly if accompanied by symptoms such as chest pain or lightheadedness, the test should be terminated. A "maximal" test is one to exhaustion. For pediatric subjects, the heart rate should exceed 180 beats/min and often will approach or even exceed 200 beats/min. The respiratory quotient should attain or exceed 1.0 if metabolic parameters are measured.

Following the study, the data are carefully analyzed, the results are compared to the known tables for the laboratory (Tables 49–4 and 49–5), and a formal report is prepared by the exercise technologist and referring cardiologist.

The incidence of exercise test complications is low even in centers where most patients are being evaluated for heart disease and arrhythmia. In over 2000 consecutive pediatric stress tests at Children's Hospital National Medical Center, there have been no

Table 49–5. Normal Exercise Data in Boys 8 to 12 Years in Age*

	Resting	*Mid Exercise*	*Maximal Exercise*
Heart rate/minute	95.5 ± 13.2 (n=44)	147.6 ± 8.70 (n=44)	185.4 ± 11.2 (n=44)
Blood pressure (mmHg) Systolic	105 ± 7.80 (n=41)	125 ± 14.8 (n=39)	134 ± 16.1 (n=33)
Diastolic	73.1 ± 8.70 (n=40)	66.4 ± 7.20 (n=33)	66.1 ± 8.90 (n=28)
Oxygen consumption (L/min)	0.302 ± (n=43)	1.17 ± 0.314 (n=44)	1.61 ± 8.90 (n=28) (n=39)
Carbon dioxide production (L/min)	0.250 ± 0.07 (n=43)	1.01 ± 0.311 (n=44)	1.55 ± 0.54 (n=39)
Minute ventilation, expiratory (L/min)	9.42 ± 3.3 (n=43)	27.7 ± 7.13 (n=44)	43.84 ± 14.1 (n=39)
Effective pulmonary blood flow, C2H2 (L/min)	3.85 ± 1.23 (n=41)	7.17 ± 2.52 (n=39)	9.08 ± 3.3 (n=34)

*Forty-four boys were tested. The average age was 10.53 ± 1.68 years; the average weight was 37.71 ± 11.40 kg; and the average standing height was 143.82 ± 12.95 cm.

deaths associated with the studies. Three patients have had ventricular tachycardia causing syncope. All were successfully treated in the exercise laboratory with control of their arrhythmia.

Exercise testing is a relatively new tool in the field of pediatric cardiology but one of increasing importance. It is useful not only in assisting physicians to make the diagnosis of heart disease, but it is the one discipline that allows for a total assessment of the patient's cardiopulmonary status during activity when many postoperative problems become apparent. Future work in exercise testing will draw upon many other diagnostic disciplines and will add to the available knowledge of the child with heart disease during the active portion of his life.

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CHAPTER 50

Nuclear Cardiology

Henry B Wiles

Blumgart, Weiss, and Yens introduced clinical nuclear cardiology in 1927 with their elegant studies on the velocity of blood flow.[1,2] They measured the circulation time from the right arm to the left arm using injections of radium C and a cloud chamber detector. Prinzmetal et al.[3] described the radiocardiogram, a time-activity curve of a radionuclide traversing the cardiac chambers. Goldring et al.[4] reported the results of 100 radiocardiograms in children with congenital heart disease. Improvements in radiopharmaceuticals and detection instruments, especially the Anger camera (see Chapter 36), led to the report by Van Dyke et al.[5] of "quantitative radioisotope angiocardiography." Further developments in pharmaceuticals, instruments, and computers during the 1970s have established nuclear cardiology as an important tool in the diagnosis and management of patients with cardiovascular disease.[6–8]

Although nuclear techniques are widely used in adult cardiovascular medicine, pediatric cardiologists have limited experience with these techniques. Nuclear cardiology is a physiologic modality that gives information on ventricular function, myocardial perfusion, and myocardial integrity. A study performed with a radionuclide is a physiologic study, not an anatomic study. Students of cardiovascular medicine are often confused by scintigraphic images because they try to visualize anatomic structures and details. An attempt to visualize a scintigraphic study as a "physiologic picture," as one would visualize a "Doppler picture," will increase the understanding and use of nuclear cardiology techniques.

Today the success of therapy for children with heart disease is measured not only in terms of survival or lifestyle, but also in terms of myocardial function and preservation; therefore, nuclear cardiology is important in the evaluation and management of children with heart disease. Pediatric nuclear cardiology is not simply determination of shunt flow; it is the evaluation of global and regional myocardial integrity.[9–12] A nuclear cardiology study is noninvasive and repeatable on an outpatient basis for serial evaluation.

This chapter presents the current techniques and indications for pediatric nuclear cardiology investigations. There are six types of studies available for the child with heart disease.

1. Blood pool imaging, usually done with technetium-99m (^{99m}Tc), gives information on right ventricular and left ventricular function.
2. Myocardial perfusion imaging with thallium-201 (^{201}Tl) investigates myocardial perfusion.
3. Infarct-avid myocardial scintigraphy, using ^{99m}Tc pyrophosphate, localizes recent myocardial infarction.
4. Tracer flow imaging, again using ^{99m}Tc, allows evaluation of blood flow patterns and velocities, including determination of left-to-right shunt flow.
5. Vascular perfusion imaging, using ^{99m}Tc labeled to macroaggregated albumin (MAA), qualitates organ blood perfusion, such as lung perfusion or determination of right-to-left shunts.
6. Inflammatory disease imaging, using white blood cells labeled with gallium-67 (^{67}Ga) or indium-111 (^{111}In), detects myocardial or pericardial inflammation.

BLOOD POOL IMAGING

Blood pool imaging assesses cardiac performance. Ventricular function is assessed by evaluation of wall motion, global and

regional ejection fraction, absolute volume, cardiac output, phase analysis, filling time, and regurgitant fraction. All of these parameters are available at rest and at peak exercise stress. Determination of volume and ejection fraction is based on the count density of radioactivity and not based on geometric assumptions. This count-based method of quantitation is theoretically superior to geometric models.

Two methods for blood pool radionuclide angiocardiography (RNA) are equilibrium studies, known as multiple gated acquisition (MUGA), and first-pass studies. Each method has advantages for both adults and children, while some advantages are unique to children. Either method alone is adequate for RNA assessment of heart disease, but ideally, both methods should be available in order to provide the maximum evaluation of children. Table 50–1 lists the advantages of each method. The main advantages of first-pass RNA in children are temporal separation of small structures (especially important for right ventricular assessment), shunt quantitation, and lower radiation dose with development of short-lived radionuclides.

EQUILIBRIUM RADIONUCLIDE ANGIOCARDIOGRAPHY

Technique

Technetium-99m bound to either albumin or red blood cells (RBCs) is used for equilibrium RNA. Both in vivo[13] and in vitro[14] methods are available for binding ^{99m}Tc to the patient's RBCs. The in vitro method requires removing a small sample of blood from the patient, attaching ^{99m}Tc to the RBCs using a commercially available kit, and injecting the labeled blood back into the patient. The in vivo method requires an injection of stannous pyrophosphate (tin) to form an RBC-pyrophosphate complex. The dose of stannous pyrophosphate is based on the patient's weight (Table 50–2), with a maximum adult dose of 3.5 mg. Fifteen to twenty minutes later, ^{99m}Tc is injected through the same intravenous line. The dose of ^{99m}Tc is again calculated according to the patient's weight (Table 50–2). A full adult dose is 25 to 35 millicuries (mCi). The in vitro method is slightly more efficient at labeling RBCs, but the in vivo method is easier and safer: there is no chance of injecting blood clots or the wrong blood specimen.

Table 50–1. Advantages of Equilibrium and First-Pass Blood Pool Methods

Equilibrium
Radionuclide bolus not important
Any vein used for injection
Multiple views from one injection
Camera easy to position
Data available for hours (exercise, intervention)
Conventional Anger camera used
Better spatial resolution
Short processing time (5 to 20 min)
Phase analysis
Left ventricular volumes more reliable
First-Pass
Short acquisition time: patient cooperation, exercise staging
Temporal separation of structures in all views
Right ventricular performance assessment
Higher photon flux for better statistical accuracy
Real-time tracer flow analysis
Shunt detection and quantification
Individual heart beats analyzed

Table 50–2. Dosage Schedule Based on Patient Weight

Weight (kg)	*Multiplier for Adult Dose*
2	0.09
3	0.12
4	0.14
5	0.17
6	0.19
7	0.21
8	0.23
9	0.25
10	0.27
15	0.36
20	0.44
25	0.51
30	0.58
35	0.65
40	0.71
45	0.77
50	0.83
55	0.89
60	0.95
70	1.00

Imaging the cardiac chambers requires a conventional Anger camera with a standard field-of-view crystal (approximately 10 in. in diameter). A large field-of-view camera (20 in.) may be necessary for studies that include both lung fields. A general purpose parallel hole collimator, with or without slants (see Chapter 36, Fig. 36–11), is used for most studies. The slant hole collimator can improve left atrial–left ventricular separation. An infant with a small heart may require a pinhole collimator (Fig. 50–1) to enlarge the structures for accurate measurements.[15] A pinhole collimator has low sensitivity and requires a long acquisition time of 6 to 8 min. Patient cooperation during this acquisition is extremely important since motion artifact is magnified.

A gating mechanism using the patient's R wave is necessary to acquire an equilibrium study. A computer divides the cardiac cycle (R wave to R wave) into nearly equal segments; the number of segments (generally 16 to 30) depends on the software supplied with the camera. The R wave triggers the camera, opens the "gates," and begins acquisition. The computer stores all radiation events occurring within each segment of the cardiac cycle. All counts recorded in the first segment of all triggered cardiac cycles are combined into one picture (Fig. 50–2). Likewise, all counts in segments 2,3,...N are added into one picture for that segment. The final "representative" cardiac cycle is a composite of several hundred heart beats. The number of heart beats used to make the composite picture can be based on time (e.g., 2½ minute acquisition), count density (acquisition continues until a predetermined number of counts are recorded), or simply a predetermined number of beats. An R-to-R interval that varies by greater than 10 to 20% is rejected by the computer. Any cardiac rhythm that has a widely varying R-to-R interval, e.g., bigeminy, makes gated equilibrium studies difficult or impossible. In this situation, list mode acqui-

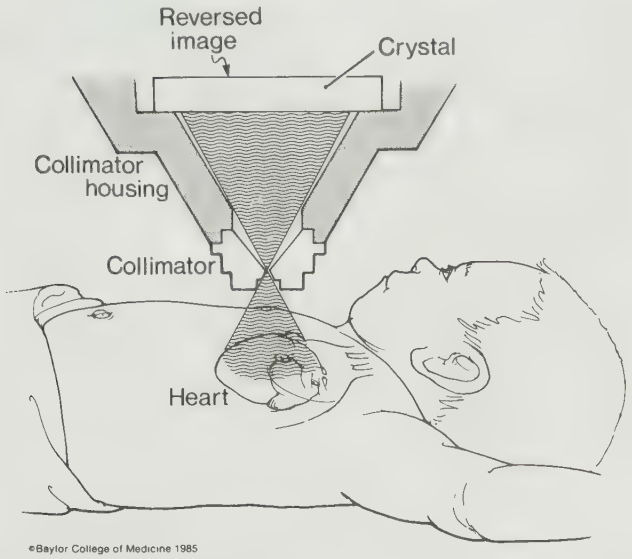

Fig. 50–1. A pinhole collimator magnifies small structures with a minimum of distortion. The small heart of an infant is often best imaged with this collimator. Since there is only one hole for gamma rays to enter, long acquisition times are required. Patient cooperation often requires mild sedation.

sition can be used to analyze individual, operator-determined heart beats.

Images are usually obtained in the anterior, 45° left anterior oblique (LAO), and 70° left anterior oblique positions. The anterior view shows the apex and anterolateral walls of the left ventricle. The 45° LAO view usually provides the best separation of right and left ventricles. The septal, inferoapical, and inferolateral walls are seen on this view. Children with complex congenital heart disease often require individualization of this view to maximize ventricular and atrial separation. The 70° LAO projection brings the inferior and anterolateral walls into view.

The data collected during an equilibrium study are stored in frame mode or list mode by a dedicated computer. Disk storage is helpful in a large center since studies can be analyzed at a different work station while additional studies are collected. The disk storage can then serve as an archival system for later retrieval of records.

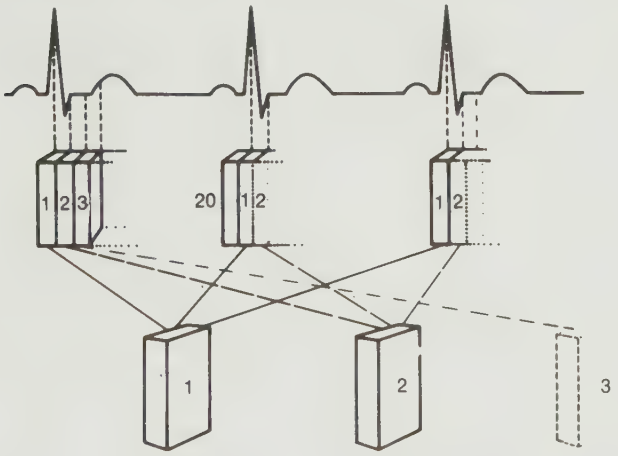

Fig. 50–2. A multiple gated acquisition (MUGA) study requires equilibrium of the radionuclide throughout the blood pool and a constant R-to-R interval. All radiation events in frames 1,2,...*N* are added into one "composite" image. This image is sequenced with subsequent "composite" images to form a representative cardiac cycle. The first frame is triggered by each successive R wave. (Holman, B.L., and Parker, J.A.: Computer Assisted Cardiac Nuclear Medicine. Boston, Little, Brown, 1981. Reprinted with permission.)

Functional Assessment

Ejection Fraction

The data collected during an equilibrium RNA study are manipulated by a computer program with operator intervention. Frames representing end diastole and end systole are examined separately by drawing regions of interest (ROI) around the ventricle (Figs. 50–3 and 50–4). Total radiation counts in the defined ROI are calculated after appropriate background subtraction. Ejection fraction (EF) is determined by:

$$EF = \frac{EDC - ESC}{EDC}$$

where EDC = end-diastolic counts
ESC = end-systolic counts
EF = ejection fraction

(Eq. 50–1)

Normal resting adult left ventricular ejection fraction (LVEF) is considered to be 55% or greater.[16,17] Normal children generally have a higher ejection fraction[18,19] (Table 50–3). Normal exercise

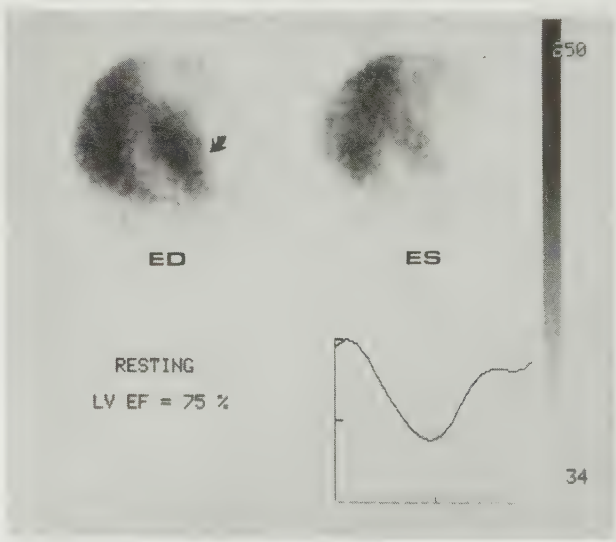

Fig. 50–3. A resting equilibrium blood pool study. The arrow indicates the left ventricle in the 45° left anterior oblique view. The ejection fraction is normal at 75%. The time–activity curve (lower right corner) from a left ventricular region of interest graphs the changing count density. The slope of this curve indicates changing volume versus time (dV/dt). ED = end diastole, ES = end systole, LVEF = left ventricular ejection fraction.

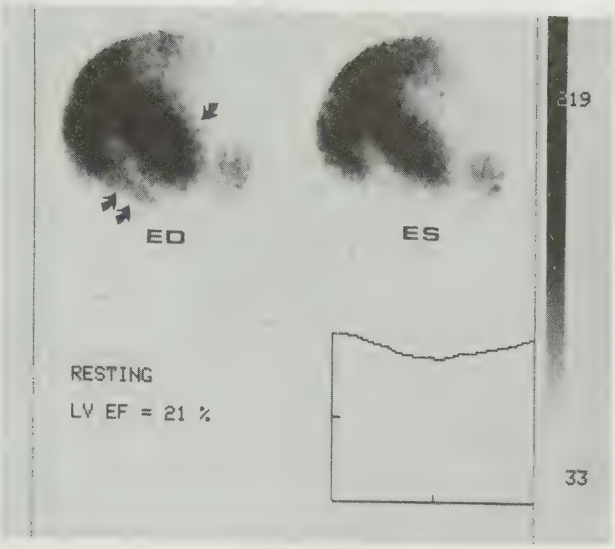

Fig. 50–4. A resting equilibrium blood pool study in a patient with dilated cardiomyopathy. The single arrow indicates a dilated left ventricle with poor contractility. The resting ejection fraction is decreased to 21%. Note that the right ventricle (double arrows) has well-preserved function. The time–activity curve (lower right corner) shows decreased ejection counts and decreased slope (dV/dt).

EF should increase by five or more ejection fraction points (e.g., 60% at rest to 65% at peak stress). Failure to increase EF with exercise (''flat response'') is mildly abnormal, and a decrease in EF is clearly abnormal.

The accuracy and reproducibility of equilibrium RNA-determined ejection fraction is well established.[20] Correlation coefficients between RNA and contrast ventriculography EF range from 0.84 to 0.93.[8,16,21–26] Intraobserver and interobserver variability is minimal[16] and less than that found with contrast ventriculography.[27] Validation of RNA-determined left ventricular (LV) and right ventricular (RV) ejection fraction in children was established by Parrish et al.[28] Correlation coefficients were 0.90 and 0.83, respectively.

Regional EF and ''first-third'' EF (percent of counts ejected in the first third of systole) may be more sensitive predictors of ventricular function than global EF.[29,30] Regional EF has been shown to correlate with regional abnormalities seen with contrast angiocardiography.[31] Since coronary arterial supply to the myocardium is regional, evaluation of regional EF may be more sensitive than global EF for ischemia. Regional EF has not been proven clinically useful in children with heart disease, but evaluation of diseases with possible regional myocardial ischemia (e.g., Kawasaki disease and anomalous left coronary artery from the pulmonary artery) may prove useful. First-third EF is best determined by first-pass RNA. Right ventricular EF can be determined by equilibrium RNA,[24,26,32,33] but overlying structures produce less accurate results. First-pass RNA is the preferred method in our laboratory for RVEF determination.

Table 50–3. Mean RVEF and LVEF in Children[19]

Age (yr)	*RVEF (+SD)*	*LVEF (+SD)*
<1	0.54±0.09	0.68±0.13
1–5	0.53±0.07	0.62±0.09
6–10	0.52±0.05	0.69±0.08
11–15	0.54±0.03	0.65±0.09
16–20	0.53±0.06	0.70±0.08

Cardiac Output

Absolute end-diastolic volume and end-systolic volume are calculated from the count density in the left ventricular ROI when compared to the count density in venous blood. The theoretical basis for this comparison is that the known concentration (count density) of radioactivity in venous blood must be proportional to the concentration and volume of blood in the ventricle. Cardiac output is determined by multiplying stroke volume (end-diastolic volume minus end-systolic volume) and heart rate. Validation of equilibrium RNA determined ventricular volumes and cardiac output has been established when compared to contrast angiocardiography,[34–36] thermodilution techniques,[37] and Fick cardiac output measurements.[38,39] This method is also validated for evaluation of right ventricular volumes in children,[40] during exercise,[38,39] and with pharmacologic intervention.[37,38]

Wall Motion

Visual inspection of a cine-like continuous loop image is important in the evaluation of ventricular function. Global and regional wall motion abnormalities are appreciated at rest and during exercise.[41,42] Anterior, 45° LAO, and 70° LAO views are evaluated at rest, and 45° LAO views evaluated at peak stress. The screen used for visual inspection should have adequate contrast and brightness controls to maximize edge detection. A finger or pointer placed at the ventricular edge often helps determine whether there is significant wall motion abnormality. Hypokinesis means the wall excursion is less than normal, akinesis means no wall excursion is detectable, and dyskinesis means wall excursion is opposite of the normal pattern. Visual wall motion evaluation is subjective and should be combined with quantitative evaluation (e.g., ejection fraction or cardiac output).

End-Systolic Pressure/Volume Loops

The use of end-systolic pressure and end-systolic LV volume is considered the best method of assessing myocardial contractility independent of preload and afterload conditions.[43] Pressure/volume loops generated from absolute ventricular volumes using equilibrium RNA studies have been shown to correlate with contrast cineangiocardiographic determinations at rest, during exercise, and with drug interventions.[44–46] A major problem with producing accurate pressure/volume loops is determination of end-systolic pressure. This technique may be most applicable to children in an intensive care environment where an arterial monitoring line is in place. Therapeutic effects on contractility can be monitored serially in children after open heart surgery or in children who are critically ill.

Filling and Ejection Times

The rate of volume change versus time (dV/dt) has been suggested as a useful measure of systolic and diastolic ventricular function[41] (see Fig. 50–3). Equilibrium RNA can provide these variables from the slope of the time–activity curve. The time to peak ejection or filling and the rate of peak ejection or filling are easily calculated. The peak ejection and filling rates are standard-

ized by relating them to end-diastolic volume. Thus, rates are expressed as end-diastolic volumes per sec (EDV/sec). Bonow et al.[47] documented abnormal peak filling rates of < 2.5 EDV/sec in 91% of 231 patients with coronary artery disease. The clinical role of systolic and diastolic filling rates in children remains to be investigated.

Regurgitant Fraction

The degree of valvular regurgitation is determined by comparing the number of counts ejected from the LV (stroke counts) to the number of counts ejected from the RV. Stroke counts are determined by subtracting end-systolic counts from end-diastolic counts. The stroke count ratio is

$$SCR = \frac{LVSC}{RVSC}$$

where SCR = stroke count ratio
LVSC = left ventricular stroke count
RVSC = right ventricular stroke count

(Eq. 50–2)

For aortic and mitral regurgitation, the SCR will be large and for tricuspid and pulmonic regurgitation, the SCR will be small. The severity of aortic and mitral regurgitation has been validated in children by this method,[48,49] as has tricuspid regurgitation in children and adults.[49,50] The range for the SCR in children without valvular regurgitation is wide: 0.70 to 1.38.[49]

Phase Analysis

The time-activity curve generated from an equilibrium RNA study approximates a sine wave. Phase analysis, using Fourier transformation of time-activity curves for each pixel within a ROI, gives onset and timing of pixel-by-pixel ejection. Since regional ejection of blood must be preceded by electrical activation, phase analysis of ejection time approximates onset of electrical activation. Using list mode acquisition techniques to eliminate any irregular R to R intervals, phase analysis activation sequences have been used to evaluate accessory bypass connections in Wolff-Parkinson-White syndrome,[51,52] right and left bundle branch block,[53] ventricular tachycardia,[54] RV dysfunction after tetralogy of Fallot repair,[55] and coronary artery disease.[56] This technique requires considerable computer power and time.

FIRST-PASS RADIONUCLIDE ANGIOCARDIOGRAPHY

Technique

First-pass RNA differs from equilibrium RNA in that the radiotracer is imaged only during the first transit through the cardiac chambers and central vessels (Fig. 50–5). Imaging the first transit produces temporal separation of right and left sides of the heart, making assessment of the right ventricle more accurate. The problem of right atrial and right ventricular separation still exists, but the camera can be positioned in a slight right anterior oblique (RAO) position to maximize separation. Another major difference afforded by first transit imaging is the short acquisition time. Ventricular function is evaluated on a beat-by-beat basis. For example, peak exercise ventricular function is measured at peak exercise, not as an average of the last 2 to 3 min. of exercise obtained with stress equilibrium RNA. Disadvantages of first-pass RNA include bolus integrity, injection technique, special camera and software requirements, and unnecessary radiation exposure with relatively long-lived radiotracers (i.e., ^{99m}Tc with a half-life of 6 hours).

The bolus of radionuclide must reach the cardiac chambers in a compact form to produce statistical accuracy. This is achieved by rapidly flushing the radiopharmaceutical through a large-bore needle or catheter positioned in a relatively large vein. The best veins for use are either the external jugular vein or the right antecubital vein. Hand, leg, and left antecubital veins are generally too distal from the cardiac chambers to assure a compact bolus. Distal veins also branch during their course to the heart, resulting in a fragmented bolus. The patient should breathe quietly during the injection since a Valsalva maneuver or crying often causes the bolus to "hang up" and produce a fragmented bolus. Bolus integrity is analyzed by placing a ROI over the right superior vena cava and evaluating the time-activity curve. The bolus should be approximately 0.5 sec or less in duration. Deconvolution analysis is a mathematical method of improving the statistical accuracy of a prolonged or fragmented bolus.[57,58]

The radiopharmaceutical used for first-pass RNA is ^{99m}Tc as sodium pertechnetate or ^{99m}Tc-labeled tracers. The use of ^{99m}Tc pertechnetate requires premedication with perchlorate to block excessive uptake of ^{99m}Tc in the thyroid, salivary glands, and stomach. The dose of ^{99m}Tc pertechnetate is 15 to 20 mCi for a patient weighing 70 kg or more. A child's dose is based on body weight and calculated from Table 50–2, with a minimum dose of 2 to 3 mCi. Technetium-99m has a half-life of 6 hours and will often not disappear from the body before another first-pass is necessary (e.g., during an exercise test). Repeat studies require correction for increased background activity that reduces statistical accuracy (see Chapter 36). Labeling ^{99m}Tc to diethylenetriamine pentaacetic acid (DTPA) or sulfur colloid helps facilitate removal of the radiotracer from the blood pool by increasing urinary excretion or increasing uptake in the liver and spleen. Injection of in vitro ^{99m}Tc-labeled RBCs or in vivo labeling after stannous pyrophosphate (see previous section on equilibrium RNA techniques) can be used for a first-pass study followed by a standard gated equilibrium study.

An ideal radionuclide for first-pass RNA should have a short half-life since imaging is acquired for only 20 to 40 sec. A short-half-life radionuclide has the advantages of decreased radiation dose to the patient and rapid disappearance from the body resulting in decreased background activity. Radionuclides currently under development are gold-195m ($T_{1/2}$, 30 sec), iridium-191m ($T_{1/2}$, 5 sec), and tantalum-178 ($T_{1/2}$, 9 min) (see Chapter 36). Perhaps the most promising of these radionuclides is ^{178}Ta, since the 9-min half-life makes it easy to work with, gated equilibrium studies can be performed after each injection, and production costs are favorable. The last section in this chapter, Future Directions, provides more information on these radionuclides.

The gamma camera is usually positioned in a 20 to 30° RAO or anterior position. Acquisition occurs for 20 to 40 sec with a rate of 10 to 40 msec per frame. Data are recorded event by event or by list mode and reformatted or regrouped by the computer for visual and analytical analysis. Regions of interest are placed over the superior vena cava for bolus analysis, RV and LV for function analysis, and lungs for shunt analysis. The best method for back-

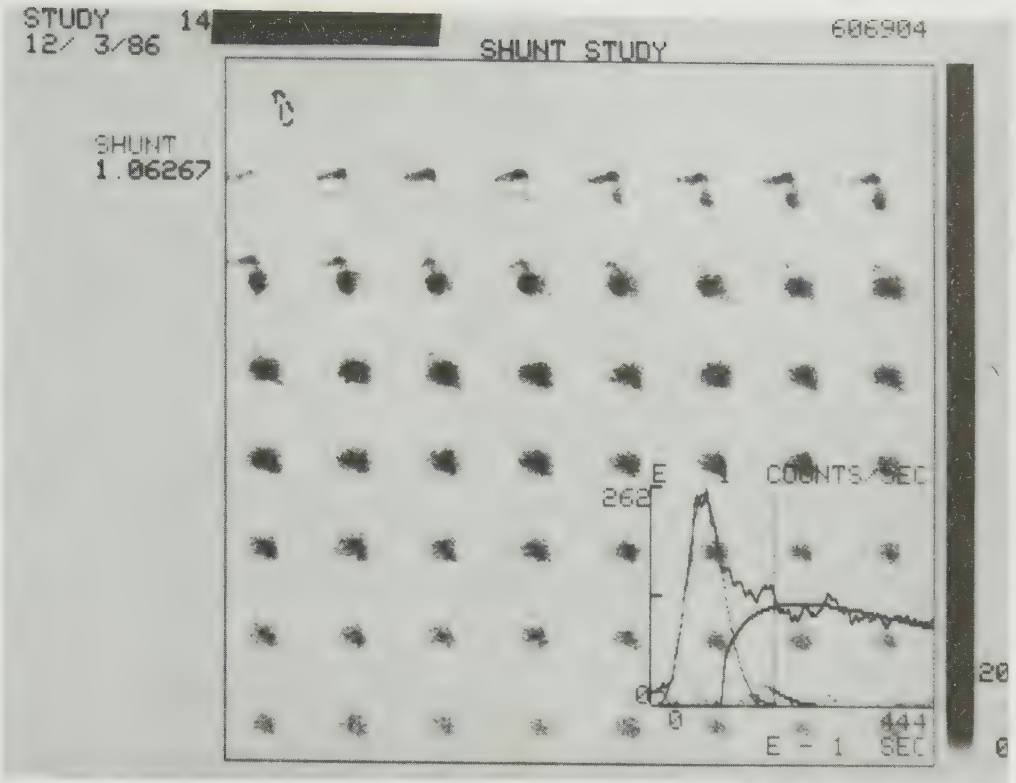

Fig. 50–5. A first-pass blood pool study for combined ventricular function and left-to-right shunt determination. The radionuclide bolus is seen traversing the right subclavian vein, right superior vena cava, right atrium, right ventricle, lungs, and left ventricle. Operator-defined regions of interest are outlined for analysis. This study demonstrated a normal Q_p/Q_s (1.06/1).

ground subtraction for LV analysis is not known, but a paraventricular region from a representative cycle is adequate.[59]

Functional Assessment

Ejection Fraction

Ejection fraction is calculated in a similar way to equilibrium RNA. Regions of interest are placed around the RV and LV, being careful not to include atria or great vessels (Fig. 50–6). End-diastolic and end-systolic counts are used for calculating the EF (see Eq. 50–1). Validation studies have documented excellent correlation with contrast cineangiography.[18,36] Normal ejection fractions in children were reported by Hurwitz et al. (see Table 50–3).[19] First-third EF may be more sensitive for detecting ventricular dysfunction caused by coronary artery disease.[37] Whether this is true for ventricular dysfunction caused by congenital heart disease is unknown.

Cardiac Output

Cardiac output determination with first-pass RNA requires that the radiotracer reach equilibrium after the first transit through the heart. Though good correlation has been found with the Fick method ($r = 0.88$),[60] equilibrium RNA-determined absolute volumes and cardiac outputs are more reliable.

Wall Motion

Visual inspection of wall motion from individual or combined beats is used for wall motion analysis. The number of counts recorded during first-pass RNA is lower than the total counts from equilibrium studies, so wall motion, especially LV wall motion, is less well defined.

Filling and Ejection Times

Calculation of the peak filling and ejection times is easily done from first pass RNA. The methodology and indications are the same as for equilibrium studies.

Regurgitant fraction and end-systolic pressure volume loops require forward stroke counts and absolute volumes. Calculations of these parameters from first-pass RNA requires many assumptions. They are best determined from equilibrium studies. Phase analysis for accurate activation sequencing also requires the statistical accuracy of equilibrium data.

Clinical Indications

The clinical indication for any blood pool RNA study is a need to know global and regional ventricular function with or without the stress of exercise. Ventricular function may be normal at rest but have limited reserve when challenged with the demands of exercise. Both equilibrium and first-pass RNA are well suited for stress studies. This advantage is in contrast to echocardiographic evaluation of ventricular function, which is technically difficult during exercise. Furthermore, echocardiographic evaluations of RV function and ventricular volumes are based on geometric assumptions, whereas RNA studies are based on count densities.

Acquired and congenital heart disease in children, including volume and pressure overload, decreased myocardial perfusion,

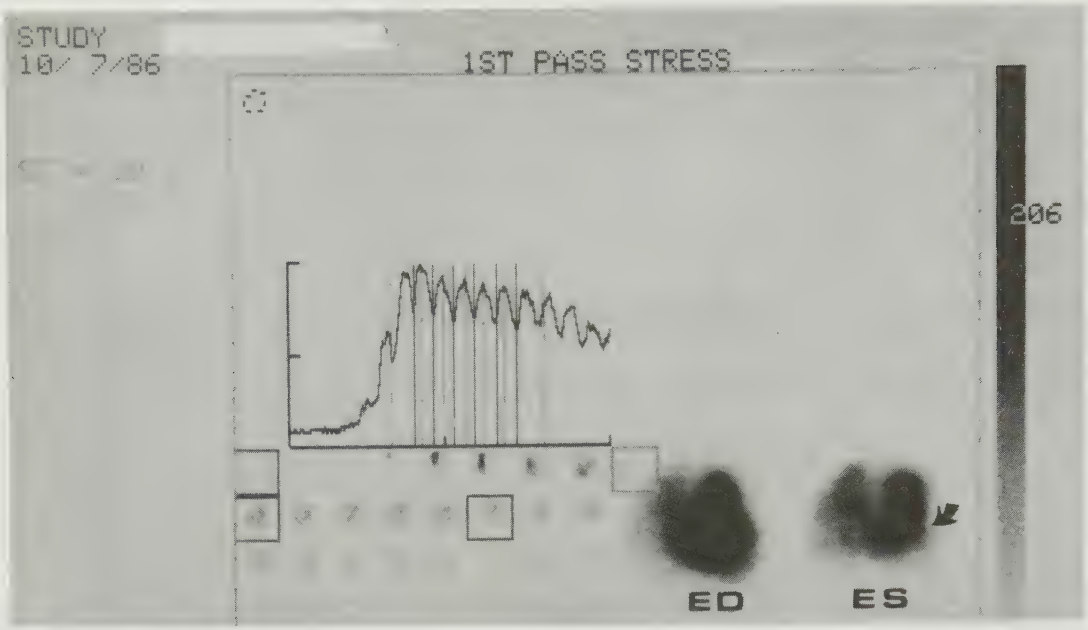

Fig. 50–6. A first-pass blood pool study during exercise stress in a patient status post tetralogy of Fallot repair. The arrow indicates the right ventricle, which has a dilated pericardial patch in the outflow tract. Right ventricular function is abnormal with an exercise ejection fraction of 29%. The time–activity curve (middle left) shows the count density in the right ventricle for each imaged heart beat. ED = end diastole, ES = end systole, EF = ejection fraction.

metabolic disturbance, cardiomyopathy, pericardial disease, systemic hypoxemia, surgical injury, and conduction disturbance, may affect ventricular function. Every child with heart disease has one or more of these features and may be an appropriate candidate for a nuclear cardiology study. Appropriate selection of patient and nuclear test requires a knowledge of the physiology of heart disease and experience with nuclear medicine compared to other modalities.

Volume Overload

Volume overload of a ventricle causes increased myocardial work, myocardial hypertrophy, and metabolic changes. Severe volume overload, especially long-standing overload, will affect ventricular function. Both RNA techniques are excellent tools for evaluating this decreased function. Since RNA may be done with exercise, this test may be a more sensitive indicator of myocardial dysfunction than either echocardiography or catheterization. Hurwitz et al.[48] showed that children with aortic or mitral regurgitation can be classified into groups with mild, moderate, and severe regurgitation and that these groups were similar to those determined by invasive means. Parrish et al.[49] further validated RNA stroke count evaluation of volume overload when compared to cineangiographic stroke volume ratios ($r = 0.88$). They concluded that RNA is an excellent tool for qualitative and quantitative assessment of valvular regurgitation in children.

Clinical Case: R.P. was a 12-year-old male with aortic regurgitation and occasional premature ventricular contractions (PVC). Echocardiography showed a moderately enlarged LV end-diastolic diameter with low-normal shortening fraction at rest. He was asymptomatic. PVCs persisted despite treatment with phenytoin. A rest-stress equilibrium RNA evaluation showed low-normal LV function at rest but a significantly abnormal response to exercise with a decreased ejection fraction. He underwent aortic valve replacement with subsequent elimination of his PVCs. The RNA test was instrumental in recommending valve replacement in this preadolescent male.

Adults with persistent small ventricular septal defects (VSD) ($Q_p/Q_s < 2:1$), surgically closed VSDs, and Eisenmenger's complex show abnormal LV function with exercise.[61] Furthermore, those patients with surgically closed VSDs had resting LV function significantly different from normal controls. Adults with VSDs and atrial septal defects (ASD) have altered mechanisms for augmenting cardiac output during exercise.[62] These findings from RNA investigations show that successful therapy for congenital heart disease may not result in a "normal" cardiovascular system. The clinical significance of these findings requires further investigation.

Nishioka et al.[63] found LV dysfunction (increased end-diastolic volume and decreased ejection fraction) in preoperative patients with tricuspid atresia. Other investigators have found persistent LV dysfunction after the Fontan procedure,[64] however, Peterson et al.[65] found a significant increase in cardiac output after the Fontan procedure. RNA evaluation of LV function after the Fontan procedure is useful in evaluating the results of surgery. The usefulness of RNA evaluation before surgery to help determine the appropriate age for the Fontan proecedure (based upon LV function) is yet to be answered.

Pressure Overload

Evaluation of LV function in the presence of pressure overload due to left-sided obstruction usually shows normal or above normal indices. The value of RNA in this setting is limited. The evaluation of a pressure overloaded RV, however, is quite useful. RNA evaluation after intra-atrial repair of d-transposition of the great arteries shows a high incidence of ventricular dysfunction. Murphy et al.[66]

showed 11 of 26 patients had abnormal RVEF or LVEF at rest while 18 of 26 had abnormal responses to exercise. In addition, Parrish et al.[67] found abnormal RV response to exercise in 6 of 11 patients and abnormal LV response in 10 of 11. Assessment of the RV in patients with congenitally corrected transposition of the great arteries (l-TGA) also showed abnormal responses to exercise in 5 of 5 patients.[67] Contrast angiographic evaluation of RV function confirmed this decreased RV function, especially in older patients with l-TGA.[68]

The results of total surgical correction of tetralogy of Fallot are generally excellent. A small group of patients, however, remain at risk for significant morbidity or mortality, probably related to ventricular arrhythmias. Identifying the entire group at risk is not yet possible. RV dysfunction may contribute to the late problems after tetralogy of Fallot repair. Reduto et al.[69] used first-pass RNA and found RV dysfunction with exercise in 13 of 16 patients after surgical repair. This RV dysfunction may be caused by surgical injury or persistent RV pressure overload.

Cardiomyopathy

Ventricular function is nearly always affected in patients with cardiomyopathy, regardless of the cause of the cardiomyopathy (see Fig. 50–3). RNA assessment of myocardial function in patients with cardiomyopathy is useful in the diagnosis, functional classification,[70] and followup of treatment efficacy. Idiopathic dilated cardiomyopathy has a variable degree of biventricular dysfunction that may be followed serially by RNA investigations.[71] Children with anomalous left coronary artery from the pulmonary artery have abnormal resting LVEF and may be followed for improvement after medical or surgical treatment.

The cardiomyopathy associated with the use of doxorubicin is often irreversible and requires termination of use of this drug. The cumulative dose necessary to produce cardiotoxicity is widely variable between patients. Serial evaluation of LVEF by RNA techniques has proven useful in determining the maximum cumulative dose for an individual patient.[72] A decrease of 15% or more in baseline LVEF predicts a high incidence of severe cardiotoxicity with clinical congestive heart failure. A decrease of 10 to 15% in LVEF does not usually result in congestive failure but probably warrants discontinuation of the drug. A decrease of less than 10% in LVEF predicts a low incidence of failure and allows for continuance of doxorubicin administration. Serial evaluation can also be used in patients with abnormal LVEF before beginning chemotherapy.[73] Exercise LVEF increases the sensitivity of detecting significant cardiotoxicity but decreases the specificity.[74] In children we begin using resting LVEF for detection of cardiotoxicity after a cumulative dose of 300 to 350 mg/m^2.

Conduction Disturbance

Nuclear imaging and phase analysis can detect and localize abnormal conduction pathways.[51–54] The ability to localize bypass tracts in Wolff-Parkinson-White syndrome may be an adjunct to electrophysiologic catheterization. The situation in which this localization may be most useful is in the patient with persistent supraventricular tachycardia after attempted surgical disruption of a bypass tract. The decision for early reoperation would benefit from the noninvasive localization of a persistent bypass tract.

MYOCARDIAL PERFUSION SCINTIGRAPHY

Technique

Coronary artery patency is important for the adequate supply of oxygen to the myocardium. Thallium-201, as thallous chloride, follows potassium kinetics. Uptake in myocardial cells is dependent on blood flow to and extraction by the myocardium. Canine myocardium under basal conditions extracts 88% of ^{201}Tl during the first transit.[75] Decreased accumulation of ^{201}Tl indicates underperfusion relative to other areas of myocardium. During exercise stress the coronary blood flow can increase by five- to sixfold.[76] Blood supply and oxygen delivery distal to an area of coronary stenosis may be adequate at rest but unable to meet the increased oxygen demands during exercise. A single dose of ^{201}Tl with immediate postexercise and redistribution rest imaging is capable of detecting exercise-induced myocardial ischemia.[77–79]

The patient should achieve maximum exercise during a standard treadmill exercise protocol (see Chapter 49). An intravenous line, established before the exercise test begins, is used for injection of 1.15 mCi/m^2 (minimum 0.15 mCi, maximum 3.5 mCi) of ^{201}Tl approximately one minute before anticipated maximum exercise effort. This early injection allows myocardial uptake of ^{201}Tl during peak myocardial blood flow. Planar imaging consists of three static views—anterior, 45° LAO, and 70° LAO—each lasting 3 to 5 min (Fig. 50–7). Within 10 min of exercise termination the patient is positioned under the gamma camera for myocardial imaging; this

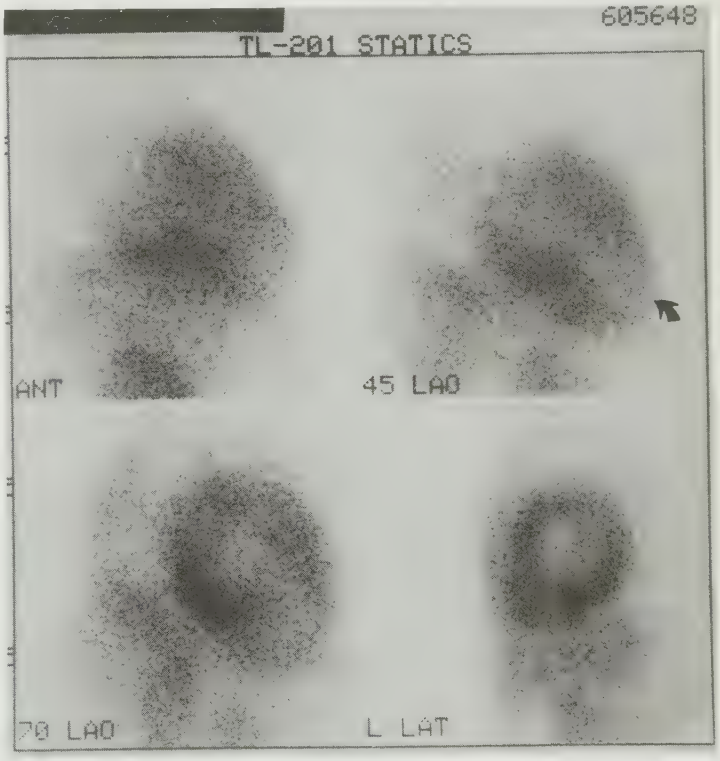

Fig. 50–7. A normal planar thallium-201 myocardial perfusion scan. Uptake is even throughout the myocardium. Note the normal decreased counts or "apical thinning" (arrow) at the left ventricular apex. Decreased counts are also normal at the mitral annulus. ANT = anterior view, LAO = left anterior oblique view, LAT = left lateral view.

image reflects the perfusion during exercise stress. Redistribution images are obtained 3 to 4 hours later in the same positions. Visual comparison of the stress and redistribution images detects relative underperfusion. A "cold spot" indicates decreased delivery of the radiotracer to that segment of myocardium. If a "cold spot" is visible on the stress image and not on the redistribution image, then stress-induced ischemia is present (Fig. 50–8). If the "cold spot" is visible on both sets of images, that region is relatively underperfused at all times and represents a scar.

Visual inspection of planar images takes considerable skill since anatomic definition is poor. This is partly due to the low energy resolution with ^{201}Tl (70 keV x-ray) (see Chapter 36) and motion of the heart during acquisition. Gating the acquisition would improve spatial resolution but make the acquisition time prohibitively long. Another method of improving the accuracy of ^{201}Tl scintigraphy is quantitative analysis of count densities in defined regions of the myocardium. Many different computer algorithms have been devised for this purpose. Quantitative analysis of count densities and washout rates generally improves the sensitivity and specificity of planar ^{201}Tl images.[80–82]

Planar imaging produces significant overlap of myocardial regions. Areas of relative underperfusion may be missed. Single photon emission computerized tomography (SPECT) produces a series of axial images, much like a CT scanner, and allows for expanded regional evaluation.[83] The gamma camera is mounted on a special gantry and rotates 180° from an RAO to LPO position. Images are obtained for approximately 25 sec at 3-sec intervals. Computer algorithms reconstruct the heart in planes aligned with the axis of the heart. Images are analogous to echocardiographic planes: parasternal long axis, parasternal short axis, and apical four-chambered views. Quantitative analysis of these images is possible with a common presentation called the "bullseye."

Thallium-201 images can be obtained at rest if the patient is unable to exercise due to age, deconditioning, or physical handicap. Resting images alone will not differentiate ischemia from a scar. Alternative methods for simulating stress-induced myocardial underperfusion have been developed using pharmacologic intervention. Intravenous dipyridamole at a dose of 0.142 mg/kg/min for 4 min is a potent coronary vasodilator, producing increases in coronary flow adequate to detect relative differences with ^{201}Tl scintigraphy.[84] This protocol is safe[85,86] and highly sensitive for detection of coronary artery stenosis.[87,88] Other methods for increasing myocardial oxygen demand include dobutamine infusion,[89] epinephrine infusion,[90] and cold pressor test.[91] We have used both dipyridamole and dobutamine infusions in infants and children who are too young to exercise. This allows utilization of the diagnostic power of ^{201}Tl imaging for detection of stress-induced myocardial ischemia. Infants and young children are sedated with chloralhydrate (50 mg/kg PO) or meperidine (2 mg/kg IM) and promethazine (1 mg/kg IM).

Clinical Indications

Myocardial perfusion scintigraphy using ^{201}Tl is indicated whenever there is a question about adequate myocardial perfusion.[92] Anomalous coronary anatomy, atherosclerotic disease, sequela of inflammatory disease (Kawasaki disease), and altered muscle func-

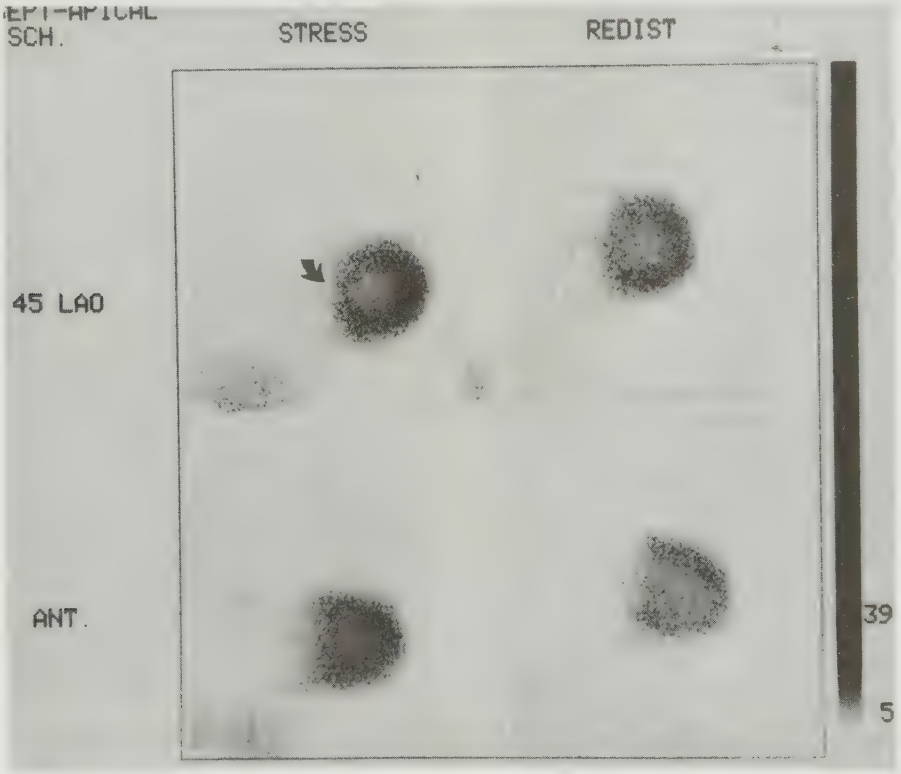

Fig. 50–8. A stress-redistribution thallium-201 myocardial scintigram showing septal ischemia and partial scar formation. The arrow indicates the septal area with decreased uptake at peak stress. With redistribution the septal area still has decreased activity compared to other areas of myocardium (scar formation) but is more homogeneous than at peak stress. LAO = left anterior oblique view, ANT = anterior view, REDIST = redistribution.

tion (cardiomyopathy and hypertrophy) can interrupt normal myocardial perfusion. The use of stress testing adds an additional dimension to myocardial perfusion scintigraphy and should be used whenever possible (see section on Techniques).

Atherosclerosis

Thallium-201 scintigraphy is widely utilized for diagnosis and management of adults with atherosclerotic coronary artery disease. Though rare in children, atherosclerosis may be accelerated in families with genetic disorders of lipid metabolism, after coronary artery aneurysms, and after cardiac transplantation. The widespread use of stress ^{201}Tl scintigraphy in children and adolescents presenting with chest pain is not indicated. Stress ^{201}Tl scintigraphy is indicated, however, in the selected young patient with severe pain, debilitating symptoms, or other physical and laboratory abnormalities of the cardiovascular system. The reassurance of a normal ^{201}Tl study may negate the need for coronary arteriography.

Anomalous Left Coronary Artery from the Pulmonary Artery (ALCA)

Patients with ALCA often present with symptoms and signs of myocardial infarction.[93] Gutgesell et al.[94] found ^{201}Tl perfusion defects in 7 of 7 children with ALCA. They also found perfusion defects in 4 of 9 children with congestive cardiomyopathy. They concluded that ^{201}Tl scintigraphy was sensitive for detecting ALCA but was not specific. They did not use any method of cardiac stress, however, and were unable to differentiate scar from ischemia. Finley et al.[95] found perfusion defects using resting ^{201}Tl images in 2 of 3 children with ALCA treated medically. Others have shown normal stress ^{201}Tl scans in patients years after surgical repair.[95,96] We have used dipyridamole and dobutamine infusions to evaluate stress and redistribution perfusion images in children with ALCA. One child had stress-induced ischemia, and one had a fixed scar. Further studies using physical or pharmacologic stress are needed to determine the best therapy for this lesion.

Kawasaki Disease

The longterm sequelae of Kawasaki disease are coronary artery aneurysm and stenosis. Approximately 1% of children with Kawasaki disease die from coronary underperfusion and myocardial infarction. Kato et al.[97] found normal resting ^{201}Tl scintigrams in children after total regression of previous aneurysms. Six of 19 children with persistently abnormal coronary angiograms had perfusion defects. Again, no method of myocardial stress was employed, and a scar was not differentiated from stress-induced ischemia.

We have applied stress to the myocardium using dipyridamole or dobutamine infusion in five asymptomatic children with coronary aneurysms.[98] Two children had stress-induced ischemia demonstrated on stress/redistribution SPECT images. One child had a fixed scar in the exact distribution of her aneurysmal coronary artery. One child had ''normal'' coronary arteries documented by angiography two years after previously demonstrated aneurysms. Her ^{201}Tl study was normal. One child with only perivascular cuffing and no aneurysm had a normal stress/redistribution study. These studies demonstrated stress-induced myocardial ischemia in certain children with coronary aneurysms who do not have evidence of coronary stenosis. One possible explanation for this finding is that the aneurysm or vessel near the aneurysm has lost the functional ability to dilate in a normal manner. The longterm prognosis for these coronary defects is uncertain.

Hypertrophy

Ventricular hypertrophy will increase ^{201}Tl uptake because of increased muscle mass and blood flow. The normal right ventricle has little or no ^{201}Tl uptake because of its thin muscular wall. Right ventricular hypertrophy due to pressure or volume overload will cause the RV to become evident on ^{201}Tl images. The clinical utility of this effect is limited. Left ventricular hypertrophy will also be evident on ^{201}Tl images. Patients with left-sided obstruction and idiopathic hypertrophic subaortic stenosis may have chest pain and ST segment depression during exercise. If these changes are due only to subendocardial ischemia, ^{201}Tl scintigraphy will not detect this perfusion defect. The resolution of ^{201}Tl images is not sufficient to differentiate subendocardial perfusion.

INFARCT-AVID MYOCARDIAL SCINTIGRAPHY

Technique

Technetium-99m stannous pyrophosphate (^{99m}Tc-PYP) localizes in irreversibly damaged myocardial tissue in a manner similar to calcium accumulation. Recent myocardial infarction can be imaged as a ''hot spot'' on ^{99m}Tc-PYP scintigrams. Technetium-99m is labeled to pyrophosphate in vitro using a commercially available kit. Injection of ^{99m}Tc-PYP is best done 48 to 72 hours after onset of infarction. Imaging with a standard gamma camera in anterior, LAO, and left lateral projections begins 3 to 6 hours after injection to allow the radiotracer to accumulate in damaged tissue.[99] Scans are graded on a 0 to 4+ scale: 0 = no tracer seen in the myocardium, 1+ = uptake less intense than rib uptake, 2+ = uptake equal to rib uptake, 3+ = uptake equal to sternal uptake, and 4+ = uptake greater than sternal uptake. Grade 2+ uptake is generally considered equivocal while 3+ and 4+ uptake are considered specific for myocardial necrosis. Free ^{99m}Tc will often label the blood pool, and one must be careful not to identify blood pool activity in the heart as a positive ^{99m}Tc-PYP scan.

Clinical Indications

Technetium-99m pyrophosphate scanning of myocardial infarction has limited use in children. Sensitivity is adequate but specificity is low. Furthermore, children rarely have acute myocardial infarction that cannot be easily diagnosed by other means. The young child or adolescent who presents with sudden, unexpected cardiac decompensation with possible acute myocardial infarction may benefit from a ^{99m}Tc-PYP scan for documentation. Identification of postoperative infarction may also be beneficial. Cardiac amyloidosis will produce positive ^{99m}Tc-PYP scans in 80 to 100% of patients with this disease.[100,101] The clinical utility of this use of ^{99m}Tc-PYP in children is unclear.

FIRST-PASS RADIONUCLIDE ANGIOCARDIOGRAPHY FOR TRACER FLOW ANALYSIS

The use of tracer flow analysis using first-pass radionuclide angiocardiography (RNA) is primarily used for left-to-right (LR) shunt detection and quantification. This use of RNA is often com-

bined with blood pool imaging for analysis of ventricular function (see section on Blood Pool Imaging).

Technique

The technique for first-pass RNA tracer flow analysis is essentially identical to the first pass technique for blood pool imaging. The frame rate during acquisition may be slower (one frame/0.5 to 1.0 sec) if ventricular functional analysis is not required. The camera must be positioned before the tracer injection so that the vascular structures of interest are imaged. Technetium-99m is the radiotracer currently used for flow studies. This radiotracer may be used alone, labeled to other chemicals for more rapid extraction from the blood pool, or labeled to red blood cells for subsequent equilibrium RNA evaluation. The new short-lived radionuclides ^{178}Ta, ^{191m}Ir, and ^{195m}Au are discussed in the section on new advances. For LR shunt studies, the gamma camera is positioned over the lungs so that primary and recirculation pulmonary flow is imaged (Fig. 50–9). Folse and Braunwald[102] devised a simple method for detecting, but not quantitating, LR shunt flow using a gamma probe over the lungs. They used a ratio of counts at peak activity (C_1) and counts at time twice of peak activity (C_2). A C_2/C_1 ratio over 0.34 was considered to represent a shunt. Two other methods of shunt detection are the area ratio techniques using extrapolation of the downslope[103] or gamma variate fit[104] (Fig. 50–10). The gamma variate method of Maltz and Treves[104] is the most accurate[105] and widely used technique. This technique requires manually drawing a region of interest encompassing one or both lung fields and generating a pulmonary time–activity histogram for analysis.

Validation of RNA-determined pulmonary-to-systemic flow ratio (Q_p/Q_s) is well documented. Alderson et al.[106] showed a correlation coefficient of 0.97 when Q_p/Q_s was determined from RNA and electromagnetic flow probes. Others have shown excellent correlation (0.71 to 0.94) when compared to calculated Q_p/Q_s using oximetry in children with LR shunts.[107–111] Deconvolution analysis will improve studies that have inferior bolus injection[57,58] and will help prevent the need for repeat studies due to injection technique. Careful analysis of time–activity curves in the right atrium and right ventricle can differentiate atrial level shunting from ventricular or ductal level shunting.

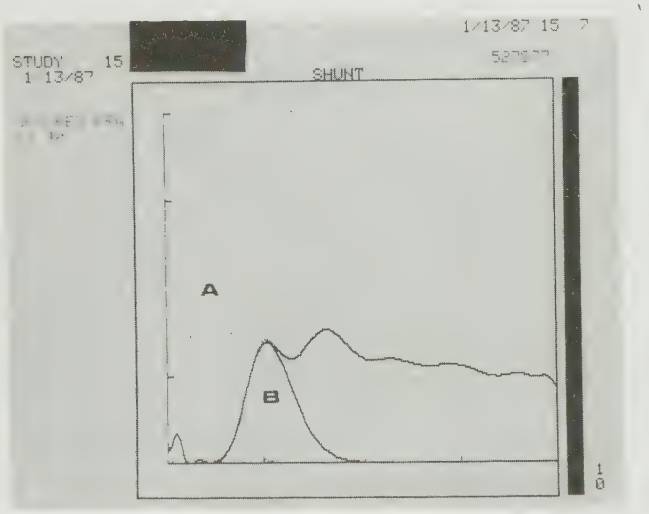

Fig. 50–9. A time–activity curve (x-axis and y-axis respectively) from a region of interest over the lungs in a patient with an atrial septal defect. The area under curve A represents the primary circulation of radionuclide through the lungs. The area under curve B represents early recirculation (left-to-right shunt) through the lungs. The pulmonary to systemic flow ratio (Q_p/Q_s) is equal to A/A − B. This patient had a Q_p/Q_s equal to 2.2/1.

A right-to-left (RL) intracardiac shunt can be detected by careful visual inspection of the tracer flow pattern. Peter et al.[112] devised a mathematical equation for quantitating RL shunts using time–activity curves over a carotid artery. Placing a region of interest over the LV and using an exponential extrapolation of the downslope of the curves can also calculate RL shunts.[9] Another method of detecting RL shunts uses radioactive particles (^{99m}Tc-macroaggregated albumin). This technique is described in the following section.

Clinical Indications

Left-to-Right Shunt

The detection and quantification of left-to-right shunt flow is the most useful aspect of tracer flow analysis[107,108,113,114,115] (Fig. 50–9). A patient with classic findings of an ASD may be sent for surgical closure without catheterization. The decision to send a patient with a suspected ASD to the operating room without catheterization depends on the confidence of the clinician in the diagnosis. The additional evidence of a calculated Q_p/Q_s by noninvasive means may be sufficient evidence to recommend surgery.

The size of shunt flow through a VSD may be followed serially by RNA. Repeat outpatient evaluations may prevent or promote early surgery depending on the calculated Q_p/Q_s. Decreasing shunt flow, however, must be carefully evaluated by physical examination. Increasing pulmonary resistance as well as a closing VSD will decrease the Q_p/Q_s. Pulmonary vascular reactivity can be evaluated in patients with pulmonary hypertension by calculating Q_p/Q_s in room air and in 100% inspired oxygen environment. Q_p/Q_s may also be measured during pharmacologic afterload reduction. The significance of a residual VSD after attempted surgical closure can be evaluated by RNA.[116] This information may help decide whether a repeat operation is necessary. Cyran et al.[117] identified a group of infants with increased risks after repair of a VSD. A $Q_p/Q_s > 3.0$ by RNA methods predicted ventricular dysfunction after operation.

Right-to-Left Shunt

The clinical utility of detecting a RL shunt by RNA is limited. Detection of a RL shunt can differentiate systemic hypoxemia caused by a pure intracardiac RL shunt versus an intrapulmonary RL shunt. A more frequent clinical question concerns the amount of pulmonary blood flow. Lung perfusion imaging is the best method for determining pulmonary blood flow (see below).

Systemic Venous Return

Peripheral venous injection will detect systemic venous abnormalities such as a persistent left superior vena cava, obstructed venous channels, hemiazygous continuation, and other venous anomalies. The resolution of these images requires that venous obstruction (e.g., after the Mustard procedure for d-TGA) be severe in order to be clearly seen.[116]

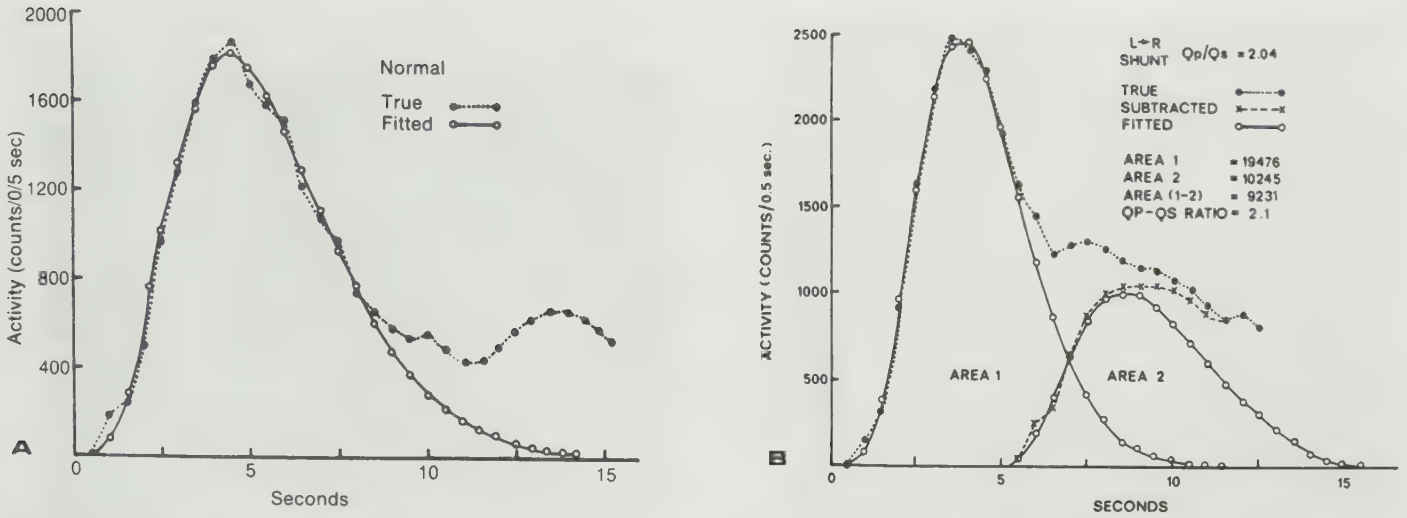

Fig. 50–10. (A) A normal time–activity lung curve showing no left-to-right shunt. The tail-end of the primary lung circulation is extrapolated using the gamma variate fit method. The "true" curve represents normal systemic venous recirculation. (B) Left-to-right shunt study. The primary circulation curve and the early recirculation curve are fitted with the gamma variate fit model. Pulmonary to systemic flow ratio (Q_p/Q_s) is determined by area 1/area 1 − area 2. (Maltz, D.L., and Treves, S.: Quantitative radionuclide angiocardiography: Determination of Q_p:Q_s in children. Circulation, *47*:1049, 1973. Reprinted with permission of the American Heart Association.)

VASCULAR PERFUSION IMAGING

Technique

The assumption in vascular perfusion imaging is that the radiotracer is stopped by the first capillary bed encountered. This assumption is generally realized if the tracer particle is 10 microns or larger in diameter. The radiotracer used for the performance of perfusion scanning is technetium-99m-macroaggregated albumin (^{99m}Tc-MAA). Dynamic tracer flow patterns can be imaged during injection of these particles. Subsequent static images outline the vascular perfusion pattern of the particles once they are trapped in a capillary bed. Qualitative blood flow volume is estimated from the relative count density in a defined region of interest. A standard gamma camera and general purpose collimator are adequate for image acquisition. A diverging collimator (see Fig. 36–11) will allow a larger field of view.

Clinical Indications

Lung Perfusion Imaging

Lung perfusion scans give qualitative images of pulmonary blood flow patterns. Perfusion abnormalities caused by absent or blocked pulmonary arteries are evident on these scans. The addition of a ventilation scan using inhaled xenon-133 gives information on ventilation/perfusion mismatch.

Right-to-Left Shunt

Detection and semiquantitation of a RL shunt is possible with ^{99m}Tc-MAA perfusion imaging (Fig. 50–11). The fraction of particles shunted right to left are trapped in systemic capillaries. The absolute ratio of pulmonary to systemic counts cannot be calculated because of geometry and attenuation of gamma rays, but an estimate of relative flows is possible. Total body counting is not necessary for the systemic blood flow fraction. A sum of brain, liver, kidney, and spleen is usually all that is necessary for systemic counts. Since microemboli of MAA are trapped in capillaries of the brain, kidney, and heart, the number of particles injected is kept at a minimum number of approximately 10,000.

Patency of Systemic-to-Pulmonary Artery Shunt

The patency and relative distribution of systemic-to-pulmonary artery shunts is possible with vascular perfusion imaging. We have often used this modality on postoperative patients to evaluate possible shunt failure due to thrombosis or mechanical obstruction and pulmonary overcirculation due to a large shunt (Fig. 50–11).[117]

INFLAMMATORY DISEASE IMAGING

Technique

Inflammatory processes are imaged with gallium-67 citrate or indium-111 oxine-labeled white blood cells (WBC). Gallium-67 localizes in areas of inflammation. Persistent body background requires delayed imaging at 24 to 48 hours after injection to visualize discrete areas of inflammation. The high-energy gamma rays from ^{67}Ga decay require that a high energy collimator be used on a standard gamma camera. Autologous WBCs labeled with ^{111}In also localize in areas in inflammation. This newer modality may be more sensitive than ^{67}Ga for inflammatory diseases and requires less time to complete.[118]

Clinical Indications

Myocarditis

Inflammatory cell infiltration of the myocardium can be detected by ^{67}Ga and ^{111}In-WBC scans. O'Connell et al.[119] found positive ^{67}Ga scans in 5 of 6 patients with biopsy-proven myocarditis. They also found nine equivocal ^{67}Ga scans in patients without myocarditis. This highlights the sensitivity but lack of specificity of ^{67}Ga scans for myocarditis. Jacobs et al.[120] used ^{67}Ga to diagnose my-

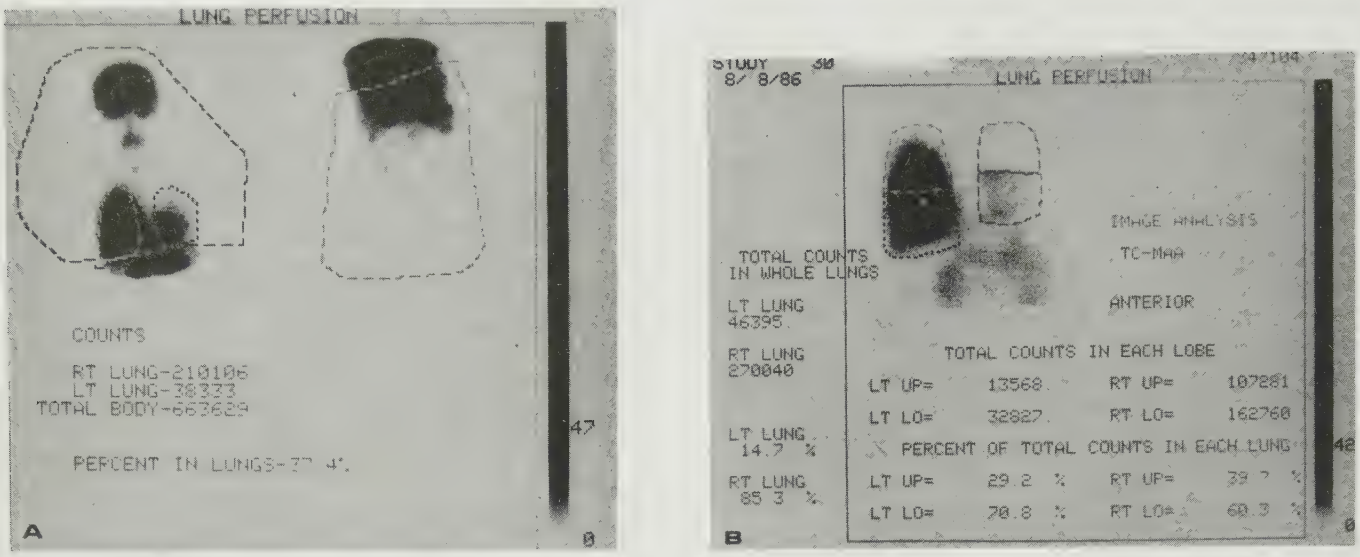

Fig. 50–11. A vascular perfusion study evaluating a surgical systemic to pulmonary shunt in a patient with pulmonary atresia and a ventricular septal defect. Technetium-99m macroaggregated albumin (Tc-MAA) injected in a systemic vein was used for this study. (A) Radioactivity is evident in the head, lungs and abdomen. Count density profiles show that 37.4% of systemic venous return flows to the lungs while 62.6% flows to the systemic circulation. (B) Anterior view of lung perfusion in the same patient. The left lung has significantly reduced perfusion (14.7%) compared to the right lung (85.3%). This patient had a thrombosed left pulmonary artery requiring surgical revision of the shunt. RT = right, LT = left, UP = upper lobes, LO = lower lobes.

ocarditis in a 15-year-old girl with Lyme disease. Williamson et al.[121] found positive ^{111}In-WBC scans in 4 of 4 patients with Kawasaki disease. They did not report the incidence of coronary aneurysms in this group. The use of ^{67}Ga or ^{111}In-WBC scintigraphy in the diagnosis and prognosis of Kawasaki disease requires further investigation.

Pericarditis

Leukocyte infiltration with inflammation of the pericardium is visible on ^{67}Ga and ^{111}In-WBC scans. Bufalino et al.[122] found positive ^{67}Ga scans in 7 of 7 patients with postpericardiotomy syndrome 14 days or longer after operation. Nine of nine patients less than 9 days after operation had negative scans. Purulent pericarditis can also produce a positive ^{111}In-WBC scan.[123]

RISKS AND BENEFITS

The risks of nuclear cardiology modalities are minimal. The largest risk is exposure to radiation. The radiation burden (see Table 36–5) to a patient is low, and this level of radiation exposure causes no known permanent effects. The risk of exercise stress is also minimal when performed under close observation in a properly equipped laboratory (see Chapter 49). The cost of an exercise ventricular performance study is considerably less than a cardiac catheterization.

The benefit of a nuclear cardiology evaluation is the availability of a safe, noninvasive, outpatient procedure that gives physiologic information on cardiac performance. Compared to echocardiography, first-pass and equilibrium RNA give more accurate information on right ventricular size and function, shunt flow, regurgitant fraction, and functional response to exercise stress. Echocardiography is far superior in delineating cardiac morphology. Myocardial perfusion imaging is not possible with any other imaging modality except positron emission tomography, the availability of which is currently limited.

FUTURE DIRECTIONS

Radiopharmaceuticals

The most promising future direction in blood pool radiopharmaceuticals is short-lived radionuclides. There are major advantages to using short-lived radionuclides: 1) the photon flux (counts/sec) is higher, giving greater statistical accuracy; 2) background activity is nearly eliminated, again giving improved accuracy; and 3) radiation dose to the patient is significantly reduced.

Tantalum-178

The half-life of ^{178}Ta (9.3 min) and the economy of the generator system make ^{178}Ta an ideal blood pool agent.[124,125] The half-life of 9.3 min makes repeat studies possible with low background activity but is long enough to allow equilibrium studies. The half-life also makes the radionuclide easy to work with in a clinical setting. The generator system is functional for at least 30 days. The radiation dose is $\frac{1}{20}$ the dose of ^{99m}Tc. The disadvantage of ^{178}Ta is the low-energy photons (55 to 65 keV) produced during decay. The low energy decreases resolution when using a conventional gamma camera. Full advantage of ^{178}Ta requires concomitant development of the multiwire proportional gamma camera.

Iridium-191m

The ultra-short half-life (5 sec) of ^{191m}Ir makes this radionuclide ideal for first-pass RNA.[109,126–128] It also delivers less radiation to the patient. The tabletop generator system is clinically useful for 1 to 2 weeks. Experimental and clinical validation of ventricular

function and shunt flow in children and adults is well established. The disadvantage of ^{191m}Ir is that the ultra-short half-life causes technical difficulties in a clinical setting. The generator is connected "in line" with the patient's intravenous line, and the generator is eluted directly into the patient.

Gold-195m

Another promising short-lived radionuclide is ^{195m}Au with a half-life of 30.5 sec.[129–132] Produced from a mercury-195m/gold-195m tabletop generator, the radiation dosimetry and clinical utility are favorable. Validation of ventricular function was established by Wackers et al.[129,130] and Dymond and colleagues.[131] The disadvantage of ^{195m}Au is the relatively short half-life of the parent ^{195m}Hg (half-life = 41.6 hours). The generator is useful for one week or less, which makes this system considerably more expensive.

Technetium-99m-Isonitrile Compounds

The new, promising radionuclides for myocardial perfusion imaging are the ^{99m}Tc-isonitriles.[133,134] These agents may replace ^{201}Tl as the radionuclide of choice for rest and stress perfusion scintigraphy. The advantages of the ^{99m}Tc-isonitriles are shorter half-life and better energy resolution. The ^{99m}Tc-isonitrile compound does not redistribute through the myocardium as does ^{201}Tl, which makes imaging technically easier.

Instrumentation

Multiwire Proportional Gamma Camera (MWPC)

The newest development in medical gamma ray detection instrumentation is the MWPC.[135,136] This gamma camera does not have a sodium iodide crystal. Detection and localization of radiation events are accomplished by a closely spaced wire grid positioned in a pressurized gas chamber. The major advantages of the MWPC are 1) high count rates (800,000 counts/sec) with little dead time, 2) high spatial resolution (2.5 mm FWHM), 3) small size, 4) low cost, and 5) ease of maintenance. (Count rate, dead time, and FWHM are discussed in Chapter 36). The MWPC is ideal for first-pass RNA with short-lived radionuclides. The major disadvantage of the MWPC is its low detection efficiency of gamma rays with energies over 80 to 100 keV. Since the gamma ray from ^{99m}Tc is 140 keV, it cannot be used with the MWPC. Consequently, new radionuclides (e.g., ^{178}Ta and ^{191m}Ir) with lower energy photons are required.

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CHAPTER 51

Nuclear Magnetic Resonance and Positron Emission Tomography—Clinical Aspects

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NUCLEAR MAGNETIC RESONANCE

Acquisition of anatomic and functional information about the cardiovascular system is a central aspect of modern cardiology. Acquisition of data about the metabolic characteristics and tissue composition of the cardiovascular system will probably assume increasing importance. None of the presently available diagnostic methods are capable of giving the clinician all the information desired. The application of nuclear magnetic resonance (NMR) techniques to the clinical evaluation of the cardiovascular system, while still very new, has already shown considerable promise as an adjunct to other diagnostic methods in the clinical assessment of cardiovascular anatomy, function, metabolism, and tissue composition.[1-6]

NMR examinations have become relatively routine in the anatomic evaluation of disorders of the central nervous system. Cardiovascular NMR has developed more slowly because the motion of the cardiovascular structures substantially increases the technical difficulty of NMR studies. However, methods of reducing motion artifact in NMR studies are becoming more sophisticated and there is reason to anticipate continued progress in this field.

This chapter will consider the currently available clinical experience with cardiovascular NMR, then discuss the practical implementation of techniques for clinical NMR evaluation, and deal with recent developments in NMR, which are likely to have useful cardiovascular applications.

Clinical use of cardiovascular NMR has been limited to imaging, with the exception of a few experimental spectroscopic studies. Although clinical applications of NMR spectroscopy may develop in the future, it is likely that many of these applications will be performed in conjunction with imaging studies because of the need for spatial localization of spectra to regions of interest.

An Overview

First, it is important to recognize the elements that compose the NMR image. An NMR image is formed from a collection of small square or rectangular areas called pixels. Many of these pixels are required to form an image, usually between 256 × 256 (65,536) and 128 × 128 (16,384). The pixels usually are displayed in shades of gray. The shading of a particular pixel is determined by the NMR signal produced by the small volume element of the subject's anatomy that the pixel represents. Such volume elements are termed "voxels."

It follows that the key to understanding NMR imaging is an understanding of how an NMR signal can be obtained from a particular voxel of the subject. There are several possible approaches, but essentially all commercial imaging systems obtain localized NMR signals by the use of magnetic field gradients and appropriately designed radiofrequency pulses. With these magnetic field gradients and radiofrequency pulses, it is possible to give the NMR-sensitive nuclei (generally, hydrogen atoms) in each imaged voxel of the subject a unique combination of rotational frequency and phase, from which their unique NMR signal can be identified. This identification is usually made by a mathematical process known as Fourier transformation.

The NMR signal produced by a particular voxel is determined by a combination of the intrinsic NMR properties of the voxel and the methods used to obtain the localized signal. Modification of the characteristics of the magnetic field gradients and radiofrequency pulses employed in NMR imaging can emphasize the effect

of some NMR properties and deemphasize others. Because different voxels of the subject will often differ in their NMR properties, it is possible to increase or decrease the contrast of NMR images by manipulation of the magnetic field gradients and radiofrequency pulses.[7,8]

Cardiovascular examinations are facilitated because the intrinsic NMR properties of rapidly flowing blood differ substantially from the NMR properties of myocardium and vessel walls. There are also differences between the intrinsic NMR properties of infarcted and normal myocardium and between the intrinsic NMR properties of atheroma and normal arterial wall. Because of the inherent three-dimensional nature of NMR imaging, many different imaging orientations are possible (Fig. 51–1).

Anatomical Evaluation

Contrast between flowing blood and the myocardial and blood vessel walls provides the basis for NMR cardiovascular imaging.[9,10] With standard spin echo images, the blood vessels appear dark while the myocardium and vessel walls have a relatively high signal intensity (Fig. 51–2). This appearance may be reversed with types of imaging sequences other than spin echo. Slowly flowing or stationary blood will also appear relatively bright on spin echo images. The generally excellent spatial resolution of NMR greatly facilitates the measurement of chamber dimensions and wall thickness. Visceral and cardiac situs is readily apparent on NMR images, and atrioventricular and ventriculoarterial connections are easily recognized. Delineation of great vessel anatomy is an important strength of NMR imaging (Fig. 51–3). The ascending and descending aorta and the distal pulmonary arteries are well defined by NMR in many cases, as are the systemic and pulmonary veins. Particularly in older patients, these structures are difficult to characterize by echocardiography. The right ventricular cavity and right ventricular anterior wall are usually clearly displayed by NMR (Fig. 51–4). These areas are of particular importance in many varieties of congenital heart disease, and again, are often inadequately visualized by echocardiography in many older patients. The left ventricle is clearly depicted in most NMR studies, and multiple orthogonal views can be obtained at various points of interest in the cardiac cycle. The atrial and ventricular septa are usually well visualized by NMR. However, the presence of small defects in the fossa ovalis and atrioventricular septal areas is difficult to ascertain reliably because the normal septal thickness in these locations approaches the limits of resolution of presently available NMR equipment. The proximal coronary arteries are often visualized on NMR studies, and in many cases it is possible to visualize their origin from the sinuses of

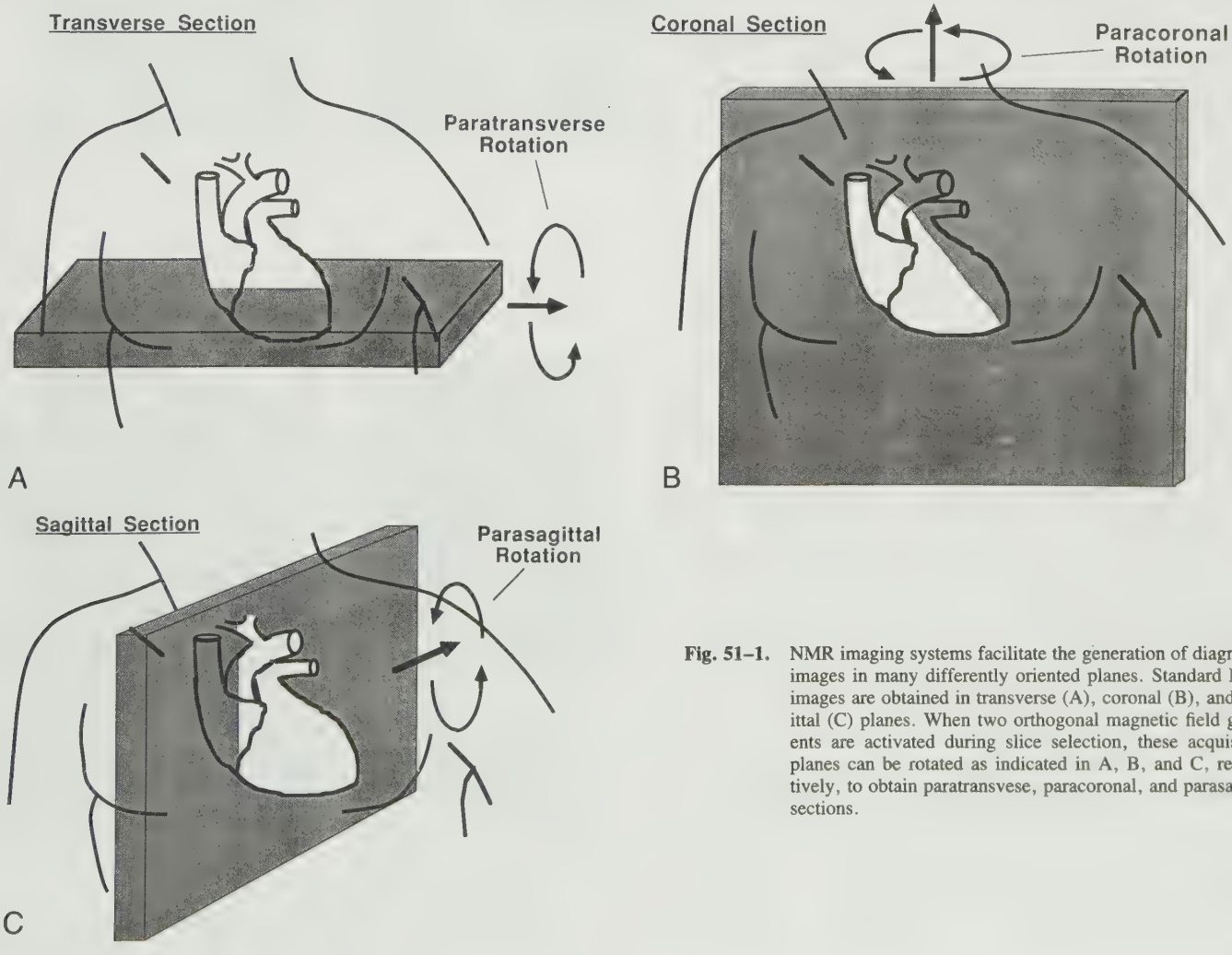

Fig. 51–1. NMR imaging systems facilitate the generation of diagnostic images in many differently oriented planes. Standard NMR images are obtained in transverse (A), coronal (B), and sagittal (C) planes. When two orthogonal magnetic field gradients are activated during slice selection, these acquisition planes can be rotated as indicated in A, B, and C, respectively, to obtain paratransvese, paracoronal, and parasagittal sections.

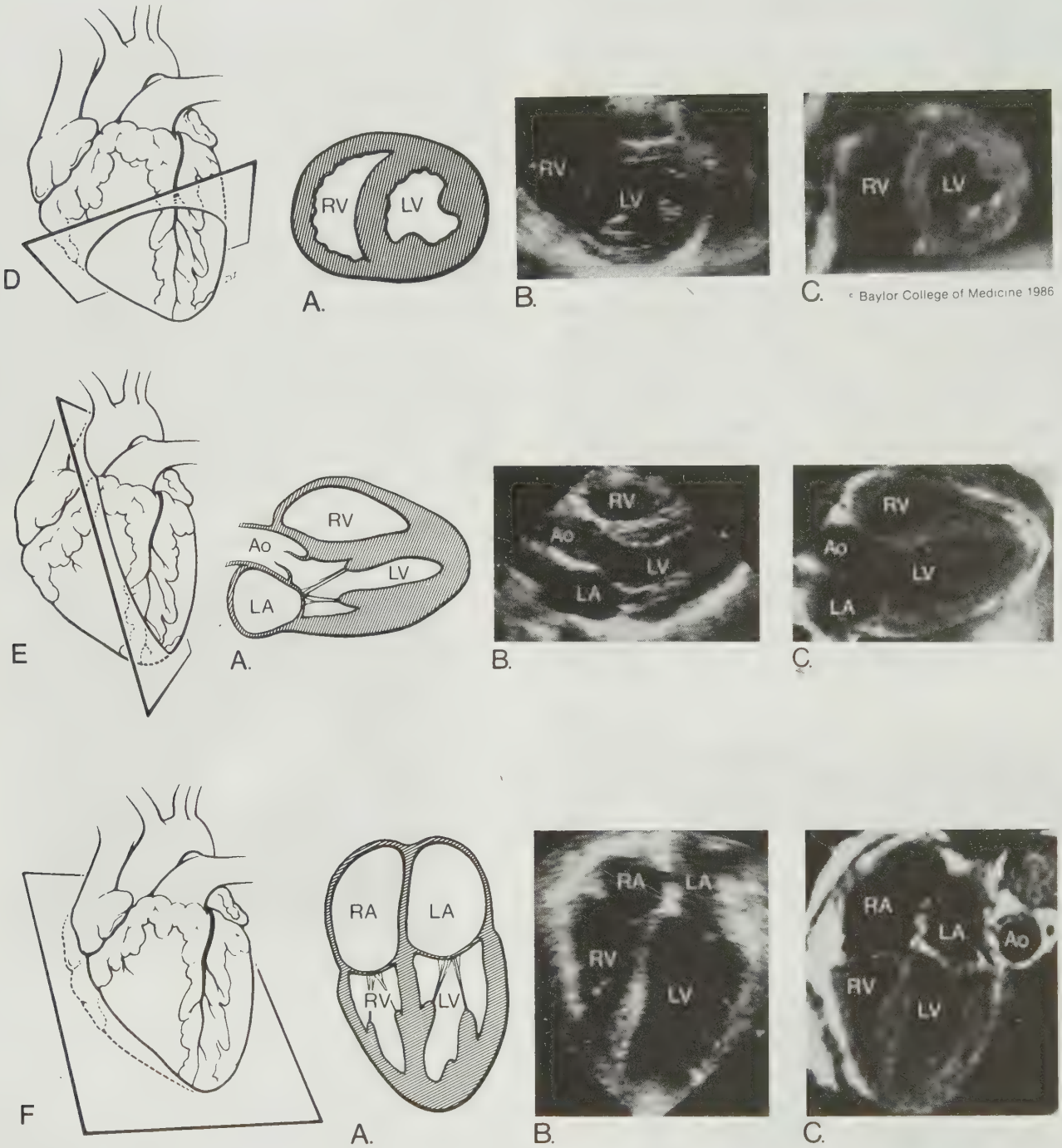

Fig. 51–1 ***continued.*** In many cases, however, planes perpendicular or parallel to cardiac structures of interest require either rotation of one of the orthogonal planes about more than one axis, or rotation of the patient. Such axial orientations can then be obtained with NMR imaging just as they can be with echocardiography or angiography. These panels illustrate NMR sections in the transverse (D), long-axis (E), and four chamber (F) orientation in comparison to illustrations and comparable echocardiographic sections. Illustrations are on the left, echocardiograms are in the center, and NMR sections are on the right. RV = right ventricle; LV = left ventricle; Ao = aorta; LA = left atrium; RA = right atrium.

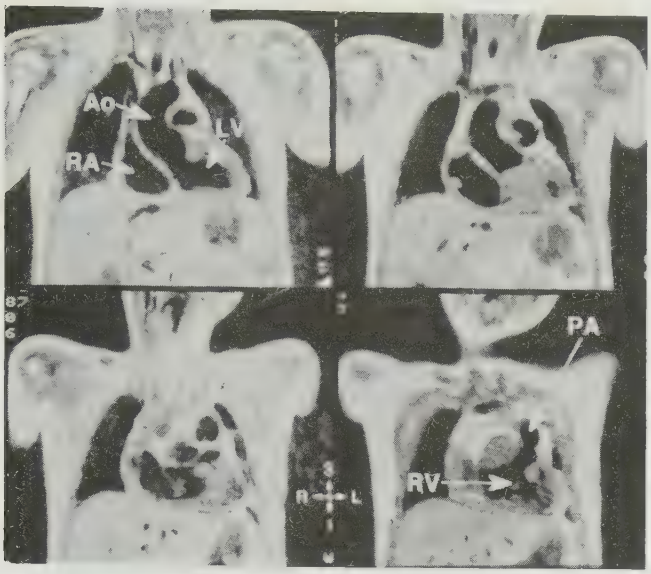

Fig. 51–2. Serial coronal sections with a progressively more anterior location clearly demonstrate cardiac structures in a postoperative patient who had undergone Rastelli repair of pulmonary atresia and ventricular septal defect and subsequent conduit replacement. The outflow tract is widely patent after the conduit revision, though the right ventricle remains hypertrophic. Ao = aorta; LV = left ventricle; RA = right atrium; RV = right ventricle; PA = pulmonary artery; S = superior; I = inferior; L = left; R = right.

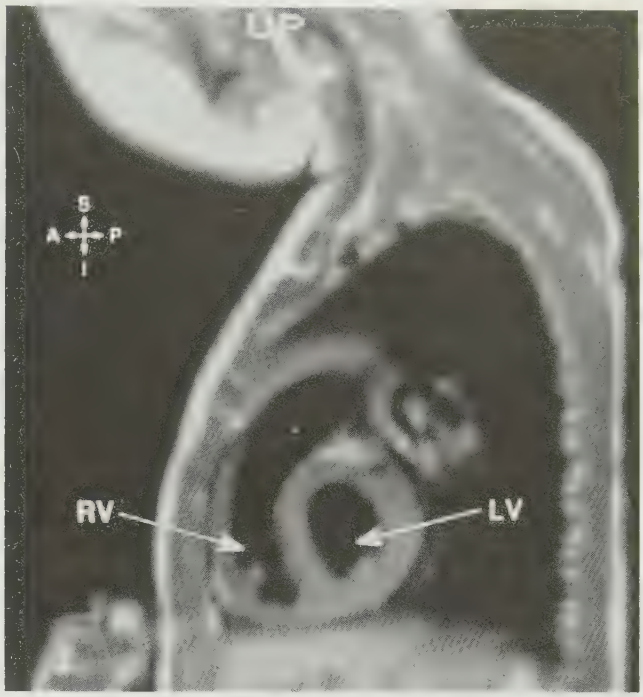

Fig. 51–4. Paracoronal spin echo image demonstrating right and left ventricles in patient with repaired coarctation of aorta. RV = right ventricle; LV = left ventricle; S = superior, I = inferior; P = posterior; A = anterior.

Valsalva. However, resolution is not yet adequate to define the presence or absence of coronary artery stenosis. Because of their rapid motion, and because they are normally very thin, the cardiac valves are inadequately defined by present NMR techniques.

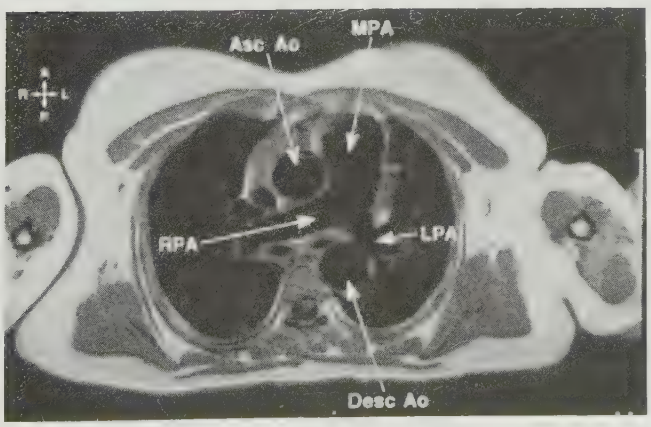

Fig. 51–3. Transverse spin echo image demonstrating the main pulmonary artery and its bifurcation into left and right branches. Asc Ao = ascending aorta; Desc Ao = descending aorta; MPA = main pulmonary artery; RPA = right pulmonary artery; LPA = left pulmonary artery; A = anterior; P = posterior; L = left; R = right.

Evaluation in Specific Cardiovascular Disorders

Coarctation of the Aorta

A considerable body of experience has demonstrated the utility of NMR imaging in evaluation of coarctation of the aorta, both before and after treatment[11–13] (Fig. 51–5). The presence of stenosis at the coarctation site can be detected and the length of the narrowed aortic segment or segments can be assessed as well as the presence of post-stenotic dilation (Figs. 51–6 and 51–7). NMR imaging can also detect the aneurysms that sometimes occur after coarctation surgery or balloon dilation (Fig. 51–8), though its sensitivity and specificity in this regard has not been determined. Although collateral vessels may be visualized on NMR studies of patients with coarctation and hemodynamically substantial obstruction to blood flow, the method for determining the adequacy of collateral formation by NMR has not been described.

Most reported studies of coarctation with NMR have used the standard spin echo technique. With this method, straight sagittal sections passing through the area of the coarctation will generally demonstrate it clearly. Paracoronal sections (which are analogous to angiographic left anterior oblique views) with appropriate angulation will usually demonstrate a larger portion of the aorta in the plane of the coarctation than will sagittal views. The sagittal views may display slightly better resolution than the angulated views, however.[14,15] Transverse sections, obtained through the de-

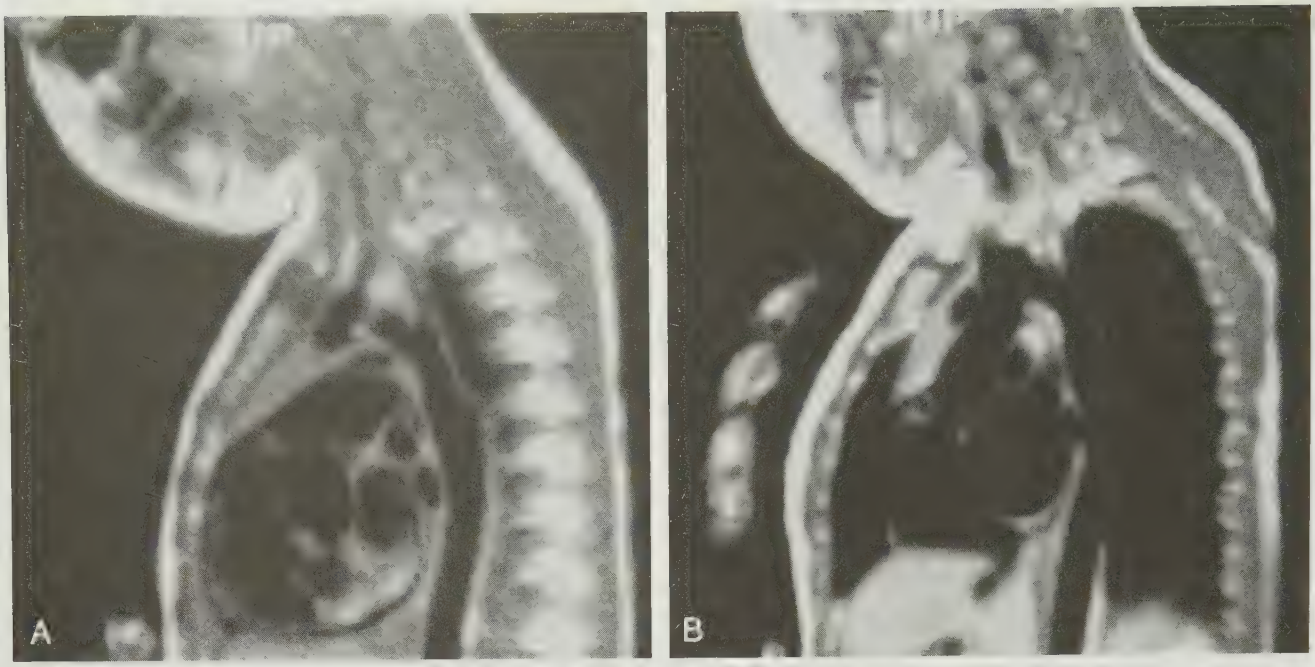

Fig. 51–5. Spin echo NMR study of aorta in a 7-year-old patient 1 yr after balloon coarctation angioplasty. Sagittal (A) and paracoronal (B) sections. Note that the ascending aorta does not lie in the sagittal plane passing through the upper descending aorta. (Orientation is as in Figure 51–4.)

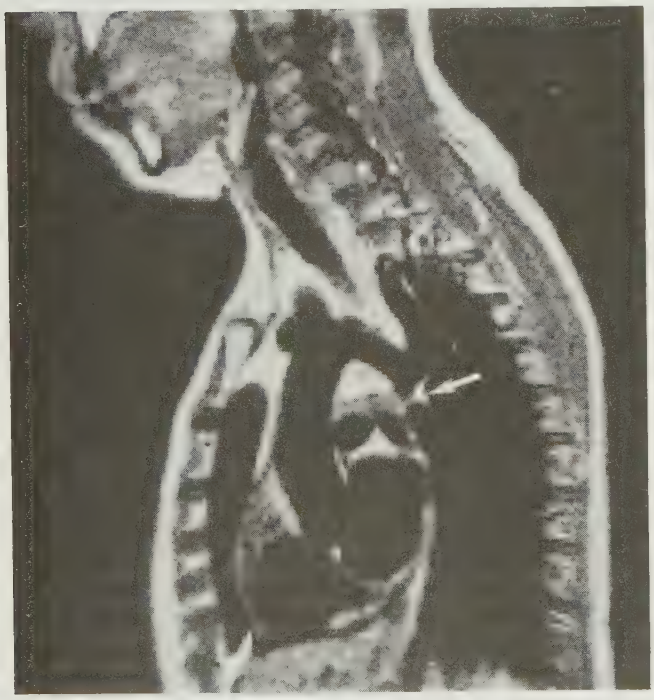

Fig. 51–6. Coarctation of the aorta demonstrated by spin echo NMR study (arrow marks site of coarctation). Paracoronal plane of acquisition. (Orientation is as in Figure 51–4.)

scending aorta at the level of the coarctation, are also useful, since they facilitate measurement of aortic diameter and provide an orthogonal imaging plane to the sagittal and paracoronal sections. Because the coarctation orifice may be extremely small and unusually oriented, it may be difficult to determine the precise diameter of the narrowest point in the coarctation with currently available NMR systems. In addition to assisting with the evaluation of the coarctation site, NMR is also a satisfactory method for evaluating the degree of ventricular hypertrophy present.

Cine NMR and NMR angiographic techniques are just now being applied to the study of coarctation. They should be particularly useful in evaluating obstruction to blood flow at the coarctation site and in assessing the adequacy of collateral formation.[16]

Marfan's Syndrome

Evaluation of Marfan's syndrome by NMR has been well described.[17] Again, NMR is an excellent tool for quantitating the aortic enlargement in this disorder. The aorta in Marfan's syndrome is characteristically enlarged in the region of the sinuses of Valsalva in relation to other portions of the aorta. Kersting-Sommerhoff and colleagues found that the ratio of aortic diameter at the sinuses of Valsalva to aortic diameter in the prearch region (upper ascending aorta) was 1.4 or greater in patients with Marfan's syndrome and 1.3 or less in patients with other causes of aortic enlargement and in normal controls.[18] NMR has shown promise as a method for detection and evaluation of aortic dissection in these and other patients with suspected aortic dissection (Fig. 51–9).[19]

The best projections for aortic evaluation in patients with Marfan's syndrome or suspected Marfan's syndrome are the transverse and paracoronal projections with the patient positioned straight supine, and the coronal projection with the patient in a 30-degree right anterior oblique position. Cine NMR and NMR angiographic

Fig. 51–7. Two paracoronal sections from a patient with coarctation of the aorta subsequent to balloon dilation. Because of the tortuous character of many vascular structures of interest, it is important to obtain multiple adjacent sections when using a tomographic imaging method. A vessel that appears to be obstructed or narrowed in one section may actually be widely patent, but with a course that carries it out of the imaging plane or slice. (Orientation is as in Figure 51–4.)

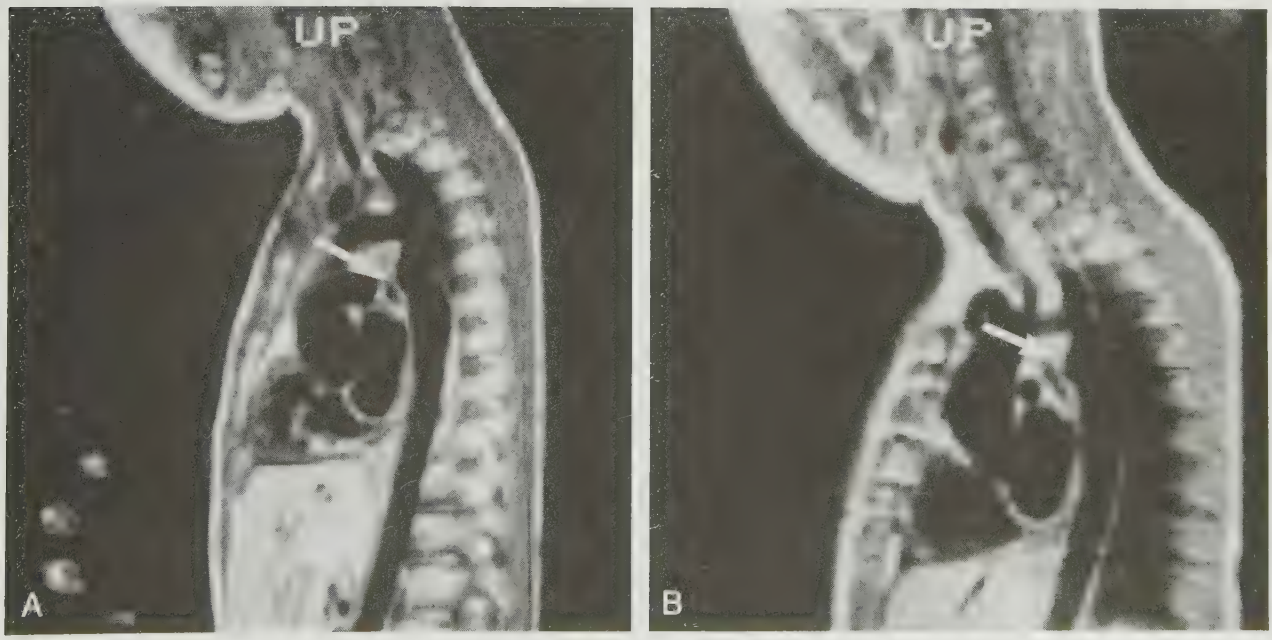

Fig. 51–8. Spin echo NMR study of aorta in an 8-yr-old patient 1 yr after balloon coarctation angioplasty. Sagittal (A) and parasagittal (B) sections are shown. A small aneurysm is present at the site of balloon dilation (arrow). (Orientation is as in Figure 51–4.)

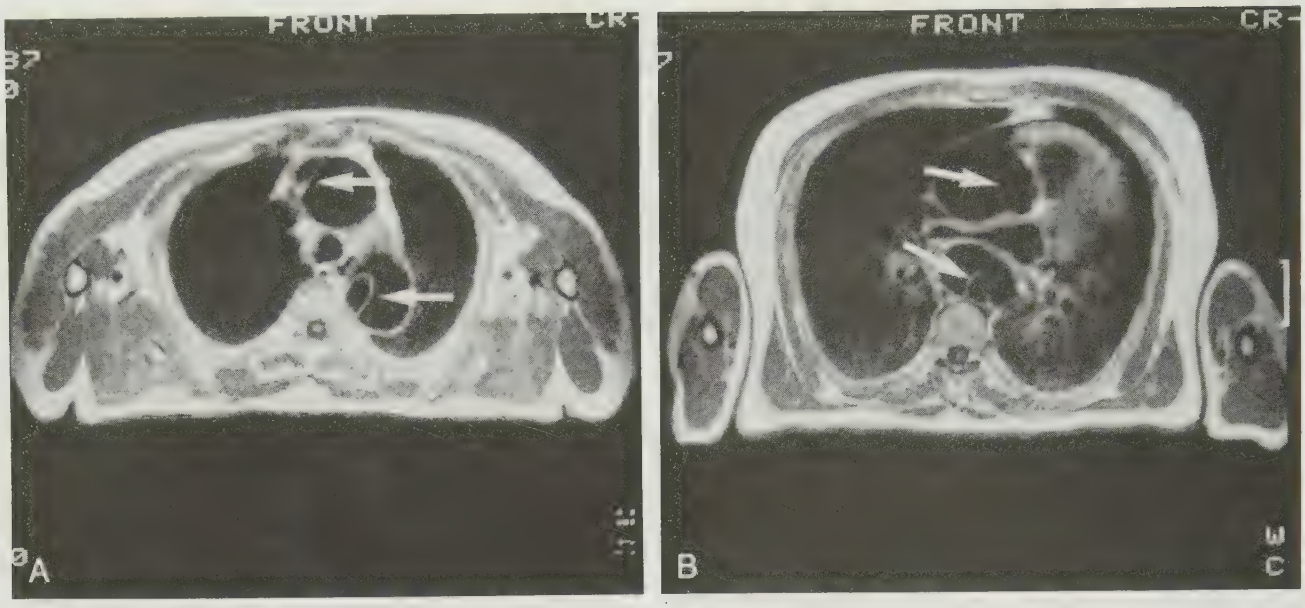

Fig. 51–9. Transverse spin echo sections demonstrating two lumens in ascending and descending aorta, findings consistent with dissection of the aorta (arrows point to location of intimal flap). Section A is obtained through the ascending and descending aorta well above the level of the aortic valve. Section B is obtained through the upper base of the heart. (Orientation is as in Figure 51–3.)

techniques promise to be very useful in Marfan's syndrome, since they should help with the evaluation of suspected aortic and mitral valvular regurgitation and may also assist in the assessment of suspected aortic dissection.[20–22]

Ventricular Septal Defects

Ventricular septal defects can be demonstrated by standard spin echo NMR imaging.[23] However, as noted above, the membranous ventricular septum is normally so thin as to be near the limit of resolution of many NMR machines.[24] Therefore one should be cautious when making the diagnosis of small perimembranous ventricular septal defect by NMR. However, large ventricular septal defects extending into the muscular septum are easily imaged with NMR (Fig. 51–10).

As is the case with angiography and echocardiography, ventricular septal defects are often displayed best if the viewing plane is either parallel or perpendicular to the plane of the ventricular septum.[25,26] In the limited number of studies so far performed, ventricular septal defect size as determined by NMR appears to correlate well with angiographic and echocardiographic results. With appropriate selection of viewing planes, it is usually possible to determine whether a ventricular septal defect is entirely muscular or whether it extends to the region of the membranous septum. It is also usually possible to classify it as being located primarily in the inlet, trabecular, or outlet ventricular septum.

The cine NMR flow studies so far performed in patients with ventricular septal defects suggest that the evaluation of velocity patterns of blood flow by NMR will be helpful in these patients.[27] NMR flow studies appear to be of particular use in localizing single ventricular septal defects and in ruling out small defects when the standard spin echo examination is equivocal. They may also prove useful for demonstrating the presence of multiple ventricular septal defects.

Fig. 51–10. Large muscular ventricular septal defect demonstrated by sagittal spin echo section. (Orientation is as in Figure 51–4.)

Atrial Septal Defects

The atrial septum is generally well visualized on standard spin echo NMR images.[28] Detection of sinus venosus, fossa ovalis, and ostium primum atrial septal defects by NMR has been described, and complete absence of the atrial septum, or common atrium, has been demonstrated as well.[29] As has been noted, the atrial septum in the area of the fossa ovalis is so thin that defects may be apparent when the septum is actually intact.

Hemodynamically significant atrial septal defects will usually be associated with right ventricular enlargement, which is easily seen on NMR images (Fig. 51–11). NMR flow studies should also demonstrate flow through the defect whenever the standard spin echo images are equivocal.[30]

Tetralogy of Fallot

NMR imaging is useful in patients with tetralogy of Fallot, both preoperatively and postoperatively.[31] In addition to the size and location of the ventricular septal defect, the right ventricular outflow tract and the pulmonary arteries can be clearly delineated. In older patients the quality of the pulmonary artery and right ventricular outflow tract images are often substantially superior to those obtainable by two-dimensional echocardiography.[32] With high-resolution systems it may be possible reliably to visualize the proximal coronary arteries and so identify the occasional patient with this disorder in whom the left anterior descending coronary artery originates from the right coronary artery and crosses the right ventricular outflow tract.

The high-quality definition of the distal pulmonary arteries obtainable by NMR in these patients can be a great help in deciding whether surgical correction is advisable in particular patients and in evaluating its results once performed. The ability of NMR to provide an accurate estimate of the extent of infundibular hypertrophy and of left and right ventricular size can be of assistance here. It does seem that patients with serious residual right ventricular hypertension after corrective surgery will have enlarged, hypertrophic right ventricles (Fig. 51–12). If they have no residual ventricular septal defect, their ventricular septum will appear flattened or will bulge toward the left ventricle. Sites of residual distal obstruction in the right ventricular outflow tract or pulmonary arteries can often be ascertained in such patients.

The pulmonary arteries are generally clearly visible on standard spin echo images performed in the transverse plane[33,34] (Fig. 51–13). It is usually advisable to obtain multiple overlapping sections to determine continuity, since the left pulmonary artery tends to lie slightly cephalad as compared with the right pulmonary artery. Properly angled sections will demonstrate the pulmonary artery bifurcation and right ventricular outflow tract, in a manner analogous to the angiographic sitting-up view, and obliquely angled sections can be useful in demonstrating the distal right and left pulmonary arteries. NMR imaging is usually not necessary to determine the mode of branching of the aortic arch, and whether it is left- or right-sided, but NMR appears to be very reliable in this regard.[35]

The limited experience currently available suggests that cine NMR and NMR angiography will substantially assist in the postoperative evaluation of patients with tetralogy of Fallot for the presence of residual ventricular septal defects, pulmonary insufficiency, and obstruction to right ventricular outflow.

Pulmonary Atresia

NMR appears to be a valuable tool in the evaluation of pulmonary atresia, particularly in older patients with this disorder,

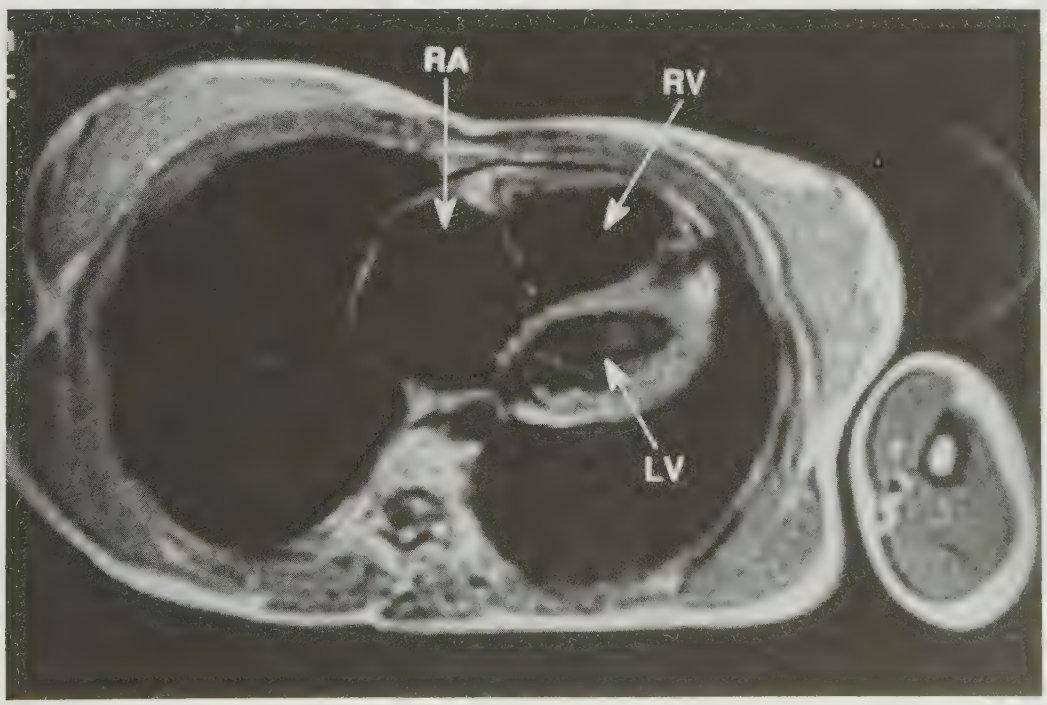

Fig. 51–11. Transverse spin echo NMR image at the midventricular level in a patient with a secundum atrial septal defect and a large left-to-right shunt. The right-sided cardiac structures are greatly enlarged. (Orientation is as in Figure 51–3.) RA = right atrium; RV = right ventricle; LV = left ventricle.

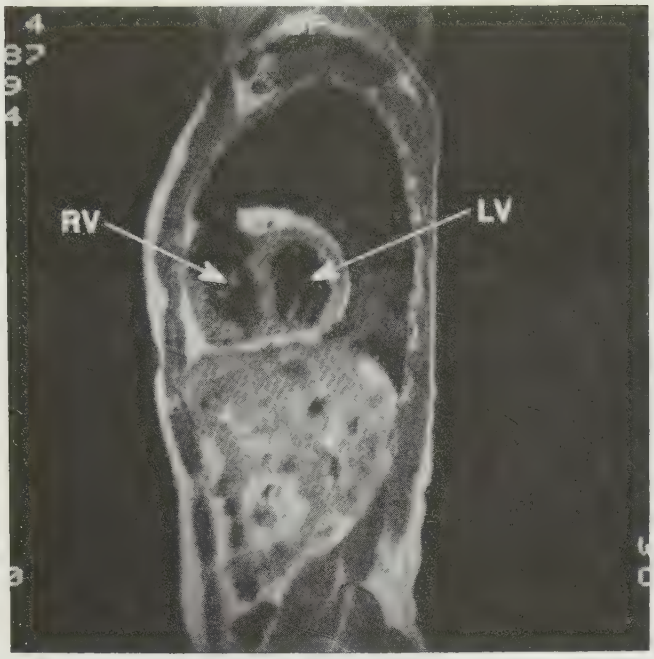

Fig. 51–12. Sagittal spin echo image of enlarged right ventricle and flattened interventricular septum in patient with right ventricular hypertension after corrective surgery for pulmonary atresia and ventricular septal defect. (Orientation is as in Figure 51–4.) RV = right ventricle; LV = left ventricle.

who have poor echocardiographic windows. Evaluation of pulmonary artery size and continuity is probably the most important part of the NMR examination in these patients, since the state of the pulmonary arteries is the most important factor in determining the suitability of these patients for corrective surgery.[36,37] The pulmonary arteries may be evaluated in the same manner as in patients with tetralogy of Fallot.

Relative ventricular sizes and degrees of hypertrophy are easily determined with NMR imaging and should be useful in the evaluation of these patients. NMR confirmation of the location and mode of branching of the aortic arch can be useful in selected cases. Many patients with pulmonary atresia have aorticopulmonary collateral vessels of substantial size, which originate from the descending aorta (Fig. 51–14). These are difficult to visualize echocardiographically and are difficult to follow on standard multislice spin echo images because of their tortuous nature. However, new methods of NMR angiography may substantially improve the noninvasive evaluation of these vessels, particularly if selective techniques can be developed.[38]

Aorticopulmonary Shunts

Surgical aorticopulmonary shunts can be clearly depicted by NMR techniques.[39] These shunts are often difficult to visualize in older patients with echocardiography. A distinction must be made between shunts with a tortuous anatomical nature, such as the Blalock-Taussig shunt and Gore-Tex shunts, and shunts that are created by side-to-side anastomoses between the aorta and pulmonary artery, such as the classic Waterston-Cooley and Potts shunts. Shunts with tortuous anatomy do not generally lie in one plane. Therefore, to follow the course of these shunts, multiple sections must be obtained in most cases when planar techniques are employed. Projective imaging with NMR angiography can be useful here, facilitating visualization of tortuous vessels along their length in one image.[40] Since direct anastomoses between the aorta and pulmonary artery are not lengthy, tortuous structures, they can usually be imaged in a single plane (Figs. 51–15 and 51–16).

Transposition of the Great Arteries

NMR imaging can clearly demonstrate the origin of the aorta and pulmonary artery and the relationship of these vessels to each other.[41,42] Although primary diagnosis of transposition complexes, both complete and corrected, can usually be made by echocardiography and other noninvasive means, NMR can have an important role in evaluating cardiovascular anomalies associated with transposition of the great arteries, both preoperatively and postoperatively, and in evaluating cardiovascular function in older patients with these disorders.[43]

In patients with transposition, NMR can demonstrate associated ventricular septal defects, atrial septal defects, and infundibular pulmonary stenosis. The relative sizes of the left and right ventricles, the extent of ventricular hypertrophy, and pulmonary artery anatomy can also be assessed. Systemic ventricular function in these patients has always been difficult to evaluate. Cine NMR could be useful here, and in assessing the systemic atrioventricular valve insufficiency often associated with transposition of the great arteries. Additionally, in patients with complete transposition who have undergone corrective surgery, NMR shows promise in detecting the obstruction to pulmonary and systemic venous return sometimes associated with intra-atrial baffle procedures,[44] and in detecting abnormalities of intracardiac and extracardiac conduits that may be associated with Rastelli repairs.

Tricuspid Atresia

While tricuspid atresia can usually be clearly demonstrated by NMR,[45] the principal role of NMR imaging in tricuspid atresia, as with transposition complexes, will probably be to evaluate these patients for associated anomalies rather than to make the primary diagnosis. NMR should be useful in evaluating the distal pulmonary arteries, pulmonary outflow tract, and aorta in these patients. In patients who have undergone the Fontan procedure or modifications of it, assessment of the atrial-to-pulmonary-artery conduit by NMR may prove helpful. Relatively poor echocardiographic windows often make anatomic evaluation of these structures incomplete.

Systemic Venous Anomalies

NMR often clearly shows systemic venous abnormalities.[46,47] Azygous continuation of the inferior vena cava is easily demonstrated with standard sagittal spin echo sections. Although azygous continuation of the inferior vena cava can usually be diagnosed by echocardiography in infants, it is more difficult to detect echocardiographically in older patients. Because the inferior vena cava does not enter directly into the heart in this disorder, cardiac catheterization from the femoral vein is complicated.

NMR readily depicts persistence of the left superior vena cava. This abnormality is usually best demonstrated in the coronal plane. With multiple coronal or sagittal sections, the course of the left superior vena cava can usually be followed to a junction with an enlarged coronary sinus, which is the usual mode of connection.

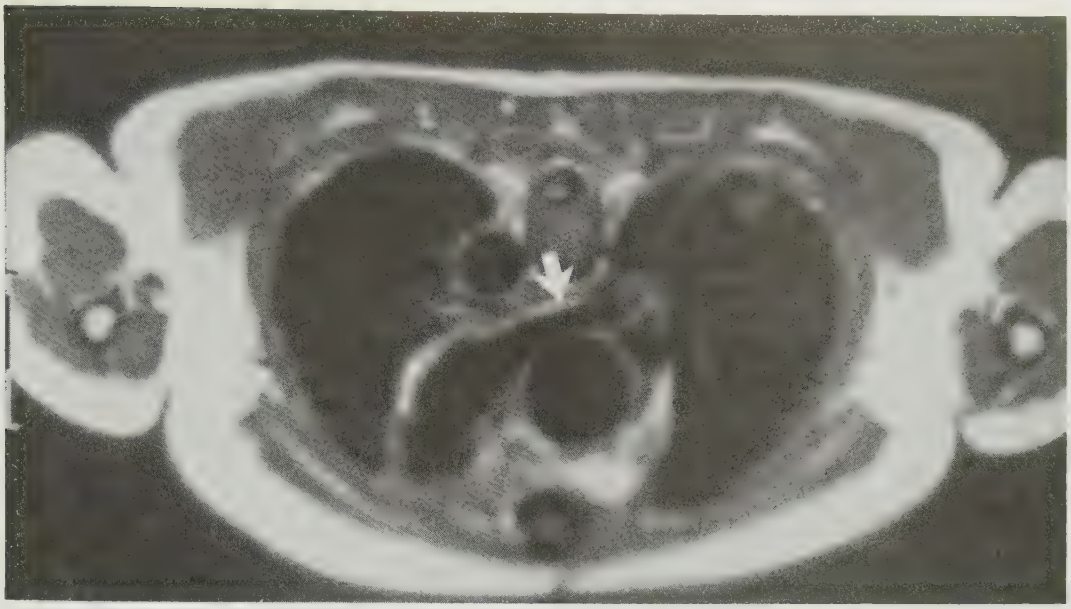

Fig. 51–13. Transverse spin echo image in postoperative patient with pulmonary atresia and ventricular septal defect, demonstrating narrowing of the right pulmonary artery (arrow).

Occasionally, a persistent left superior vena cava will connect directly to the left atrium. Diagnosis of a persistent left superior vena cava is important because its presence may complicate cannulation at the time of institution of cardiopulmonary bypass, and because in the unusual case in which its connection is to the left atrium, right-to-left shunting takes place.

Anomalous hepatic venous return is also demonstrable by NMR, and is best seen on sagittal or coronal images. Anomalous hepatic venous return to the atria, particularly the left atrium, can complicate intracardiac repair of complex congenital heart disease.

Pulmonary Venous Anomalies

The pulmonary veins can be visualized in many NMR studies, and the demonstration by NMR of several of the many abnormalities of pulmonary venous connection has been reported.[48,49] Because most patients with total anomalous pulmonary venous connection present with symptoms in early infancy, and because total anomalous pulmonary venous connection can be diagnosed in infants by echocardiography with a high degree of accuracy, NMR need not be widely employed to provide primary diagnosis

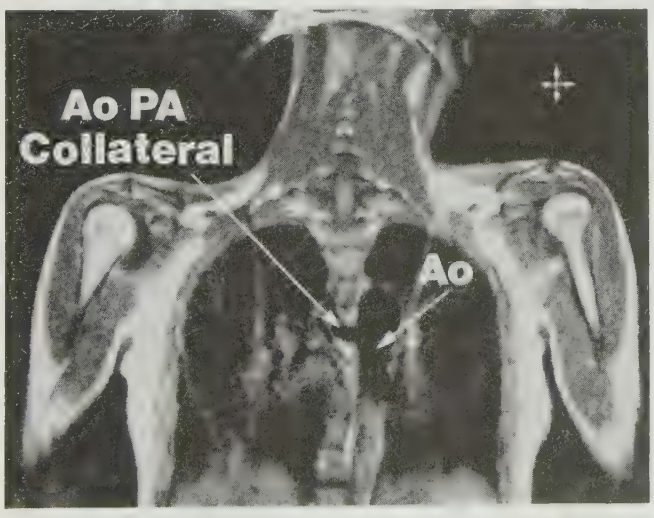

Fig. 51–14. Origin of large aorticopulmonary collateral vessel from the descending aorta in a 19-yr-old patient with pulmonary atresia and ventricular septal defect. Ao PA collateral = aorticopulmonary collateral vessel; Ao = aorta. (Orientation is as in Figure 51–2.)

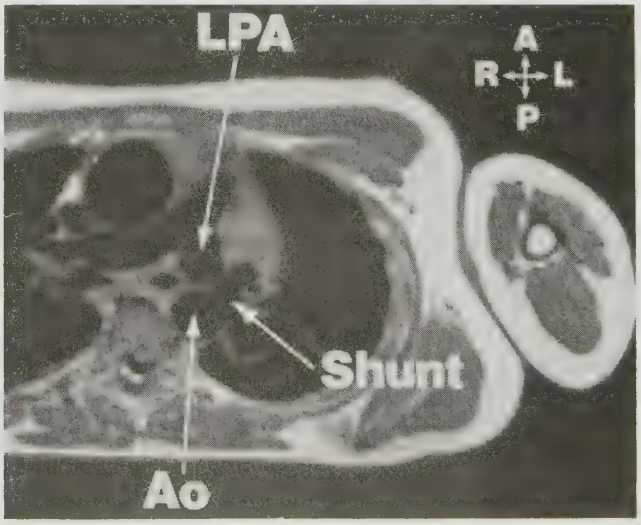

Fig. 51–15. Transverse spin echo image in a patient with severe pulmonary stenosis and a Potts' shunt, demonstrating the communication between the left pulmonary artery and the descending aorta at the site of the shunt. LPA = left pulmonary artery; Ao = aorta; shunt = Potts' shunt; A = anterior; P = posterior; L = left; R = right.

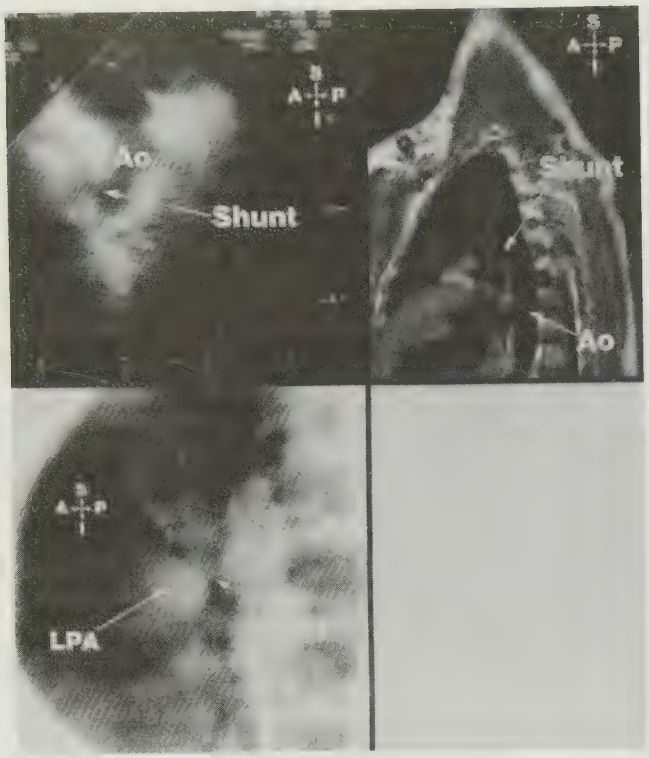

Fig. 51–16. A paracoronal spin echo NMR section, parallel to the axis of the aorta and parallel to the axis of the shunt, was obtained by using the transverse image shown in Figure 51–20 for guidance. This section is shown in the upper right-hand panel of the figure. Comparable echocardiographic (left upper panel) and angiographic (lower panel) studies of the shunt in this patient are also shown. The shunt lumen is more clearly depicted with NMR than with the other imaging methods. Ao = aorta; shunt = Potts' shunt; LPA = left pulmonary artery; S = superior, I = inferior; P = posterior; A = anterior.

in this disorder. However, NMR can be of considerable use in older postoperative patients with total anomalous pulmonary venous connection who have undergone corrective surgery. These patients may have residual stenosis at the site of the surgical anastomosis between the pulmonary venous confluence and the left atrium, and may also have stenosis of the individual pulmonary veins. In older patients, these residual defects may be difficult to visualize by echocardiography.

Partial anomalous pulmonary venous connection often presents in childhood and adolescence, and it is usually, but not always, associated with an atrial septal defect, often of the sinus venosus type. It can be corrected surgically in many instances, and if it is not detected preoperatively, patients may be left with a large residual left-to-right shunt after surgical repair of an atrial septal defect or other congenital cardiac anomaly. Partial anomalous pulmonary venous connection is relatively difficult to diagnose accurately by echocardiography in older patients, but is often demonstrable by NMR.[50] It is therefore likely that NMR will have an important role in both the primary and secondary evaluation of patients with this disorder.

The pulmonary veins and their connections are best depicted in the transverse and coronal planes.[51,52] Cine NMR techniques may facilitate quantitation of the velocity and amount of flow in individual pulmonary veins.

Atrioventricular Canal Defects

A major feature of atrioventricular canal defects—deficiency of the atrioventricular septum—is readily visualized with standard NMR imaging techniques.[53] The atrioventicular septum is best delineated by an imaging plane perpendicular to the axes of the lower atrial septum and the inlet ventricular septum. Such a plane demonstrates all four chambers of the heart, and is often termed the "four-chamber view."[54,55]

In addition to deficiency of the atrioventricular septum, abnormalities of the atrioventricular valves are present in patients with atrioventricular canal defects. These anomalies range from minor clefts to much more extensive defects, in which only a single common atrioventricular valve is present, rather than separate mitral and tricuspid valves. Because of their relatively thin structure and rapid motion, defects of the atrioventricular valves are difficult to visualize with currently available NMR techniques. However, cine NMR methods show promise for detection and quantitation of the atrioventricular valve insufficiency often associated with the structural atrioventricular valve defects. Furthermore, NMR can define many of the congenital cardiovascular abnormalities often associated with atrioventricular canal defects, such as coarctation of the aorta, pulmonary artery stenosis, pulmonary and systemic venous anomalies, and relative ventricular hypoplasia. Particularly in older patients, these associated anomalies may be difficult to define by other noninvasive techniques.

Hypertrophic Cardiomyopathy

The excellent definition of the cardiac wall provided by NMR imaging facilitates accurate characterization of ventricular hypertrophy in patients with hypertrophic cardiomyopathy[56,57] (Fig. 51–17). The highly varied spectrum of hypertrophic cardiomyopathy is well demonstrated by NMR. Some patients have hy-

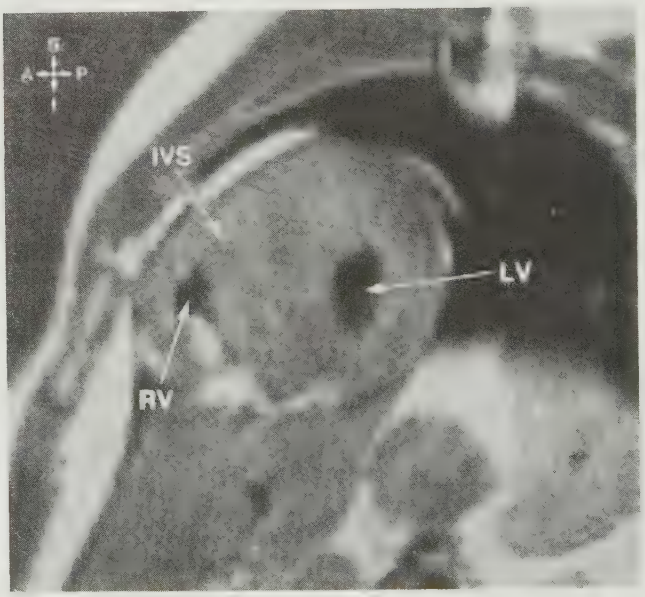

Fig. 51–17. Parasagittal spin echo NMR image in patient with severe hypertrophic cardiomyopathy. Note the prominent hypertrophy of the interventricular septum. IVS = interventricular septum; LV = left ventricle; RV = right ventricle; S = superior; I = inferior; P = posterior; A = anterior.

pertrophy of the entire ventricular septum; others have hypertrophy of the apex, the ventricular free wall, or the outlet septum. NMR and two-dimensional echocardiographic measurements of ventricular hypertrophy in these patients correlate well when adequate echocardiographic windows are available. However, a substantial number of older patients have such limited echocardiographic windows that complete ventricular evaluation is not possible by echocardiography.[58] In these patients, NMR appears to be the imaging method of choice. Echocardiography has the advantage of allowing for relatively easy estimation of pressure gradients across sites of possible obstruction through Doppler measurements of intracardiac blood flow velocity. This information is not currently available by NMR.

Cardiac Tumors

There have been several reports of identification of intracardiac and extracardiac mediastinal tumors by NMR imaging[59–61] (Fig. 51–18). When two-dimensional echocardiography and NMR have been compared, NMR has generally provided better resolution of these tumors. Many tumors have substantially different T1 and T2 relaxation parameters from surrounding tissue, making possible high contrast between normal and abnormal tissue with appropriate adjustment of pulse sequences.

Pericardial Disease

The pericardium is normally a membranous structure that usually is not resolved by standard NMR imaging techniques. On standard spin echo images, a thin line of low signal intensity separates the myocardium from the epicardial and pericardial fat.[62] This line may be produced by the small amount of fluid normally present in the pericardial cavity. Pericardial thickening, such as that present in chronic constrictive pericarditis, is readily visualized by NMR.[63,64] When constrictive pericarditis is present, the vena cava is dilated while the ventricles are relatively small. Pericardial effusions can also be clearly demonstrated with NMR,[65] and preliminary studies[66] suggest that it may be possible to obtain information about the content of the pericardial effusion (i.e., transudate, exudate, chylous nature, and presence of hemoglobin) by appropriate NMR pulse sequences (Fig. 51–19).

Cardiac Valve Stenosis and Insufficiency

Although the semilunar and atrioventricular valves are often visible on NMR images, their rapid motion generally precludes reliable structural evaluation with current techniques. However, valvular stenosis and insufficiency create flow disturbances that are readily visualized by cine NMR techniques. Quantitation of the degree of cardiac valvular stenosis and insufficiency with cine NMR is just beginning, but it shows promise.[20,67] NMR imaging also provides useful information about the extent of cardiac hypertrophy and chamber enlargement in these patients.

Congenital Coronary Artery Anomalies

Vandenbossche and colleagues demonstrated a left coronary arteriovenous fistula by NMR imaging and confirmed its presence with angiography.[68] Because the proximal coronary arteries and their origins are often visualized by NMR, it would seem that NMR diagnosis of other types of coronary artery fistulas and such anomalies as origin of the left anterior descending coronary artery from the right coronary artery, and aberrant left anterior descending artery coursing between the aorta and pulmonary artery should be feasible.

Cardiac Hypertrophy

NMR can provide detailed evaluation of cardiac hypertrophy.[69,70] NMR measurement of left ventricular hypertrophy correlates well with echocardiographic and angiographic determinations. NMR may prove to have particular importance in evaluating right ventricular hypertrophy, since the right ventricle is well defined by

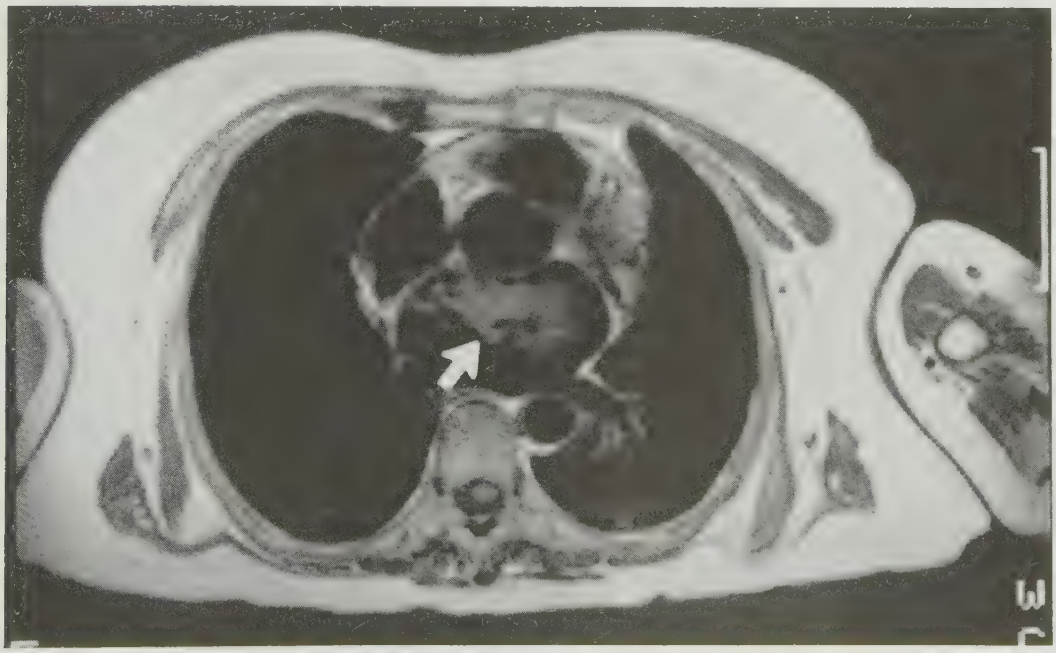

Fig. 51–18. Transverse spin echo NMR image demonstrating large left atrial myxoma (arrow). (Orientation is as in Figure 51–3.)

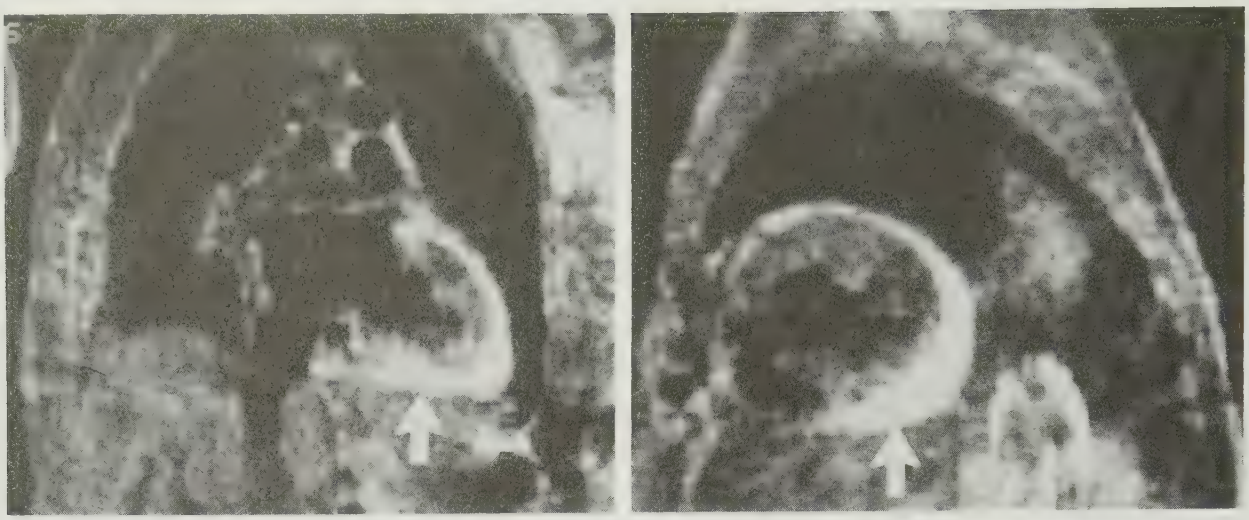

Fig. 51–19. Paracoronal (left) and parasagittal (right) spin echo NMR images demonstrating pericardial effusion (arrows) with high signal intensity. The effusion was determined to have an elevated cholesterol content. Tissues containing lipid have a low T1 and, as a consequence, tend to have a high signal intensity when imaged with the spin echo technique. (Orientations are as in Figures 51–2 and 51–4, respectively.)

NMR imaging but is often difficult to evaluate by echocardiography.[71,72] Common lesions in which ventricular hypertrophy is well defined by NMR include valvular heart disease and pulmonary and systemic hypertension.

Dilated Cardiomyopathy

The presence of a dilated cardiomyopathy is readily detected by NMR (Fig. 51–20). Cardiac chamber sizes are easily evaluated by standard NMR imaging methods. Volume determinations by magnetic resonance imaging correlate well with other methods.[73,74] Cardiac function can also be evaluated, as discussed below, by either the multislice imaging method or with one of the newer cine NMR techniques.[75] However, NMR contrast between cardiac walls and intracavitary blood is often diminished in dilated cardiomyopathy because of relatively slow intracardiac blood flow. Since echocardiography can also evaluate cardiac chamber size and function, the role of NMR imaging in patients with dilated cardiomyopathy remains to be determined. Possible areas in which NMR imaging may provide information not available by echocardiography in these patients include evaluation for segmental cardiac dysfunction, evaluation of possible intracardiac thrombus in locations not well visualized echocardiographically, and assessment of patients with poor echocardiographic windows. As discussed below, NMR spectroscopy may be of use in evaluating the cause of dilated cardiomyopathy.

Cardiac Transplantation

Initial results of NMR imaging in experimental animals and in patients that have undergone cardiac transplantation suggest that transplanted hearts being rejected have elevated T1 and T2 relaxation values in comparison with hearts not being rejected.[76,77] NMR imaging could potentially facilitate noninvasive monitoring of these patients for rejection and thus reduce the need for cardiac biopsies. NMR spectroscopy could also prove to be useful in evaluating patients with a heart transplant, since experimental results suggest that transplant rejection is associated with a substantial decrease in myocardial creatine levels.[78] This area needs further study.

Ischemic Cardiac Disease

NMR imaging can assist in the evaluation of many aspects of ischemic cardiac disease. Since ischemic atherosclerotic vascular disease affects different segments of the myocardium in different manners depending on the blood supply to these segments, the ability of NMR imaging to assess segmental cardiac function is particularly useful.[79] Segmental cardiac function can also be assessed by echocardiography, but the relatively unsatisfactory echocardiographic windows in adult patients sometimes make evaluation of all cardiac segments infeasible.

Ischemic periods too short to cause necrosis do not alter the measured T1 and T2 relaxation times of the myocardium. Thus routine imaging with spin echo pulse sequences alone is unable to detect the presence of myocardial ischemia. Myocardial wall thinning and altered motion in areas of ischemia may be visualized, however, and ischemia may be inferred when such changes are detected. However, new NMR imaging techniques sensitive to flow may eventually allow evaluation of myocardial perfusion as a means of predicting ischemia,[80] and spatially resolved NMR spectroscopy may become a useful tool for detection of myocardial ischemia.[81]

Acute Myocardial Infarction

Acute myocardial infarction causes an increase in both the T1 and T2 relaxation times of the infarcted myocardium.[82–85] The relaxation time changes associated with acute infarction are caused by a combination of factors, including myocardial edema, lipid accumulation in the myocardium, and as yet undefined biochemical changes. Spin density of the myocardium also increases, probably as a result of increased water content. The changes generally are not clearly apparent until 3 to 4 hr after coronary occlusion. Coronary reperfusion tends to accentuate the increase in relaxation times and spin density. With appropriately designed pulse sequences, NMR images will reflect the relaxation time changes

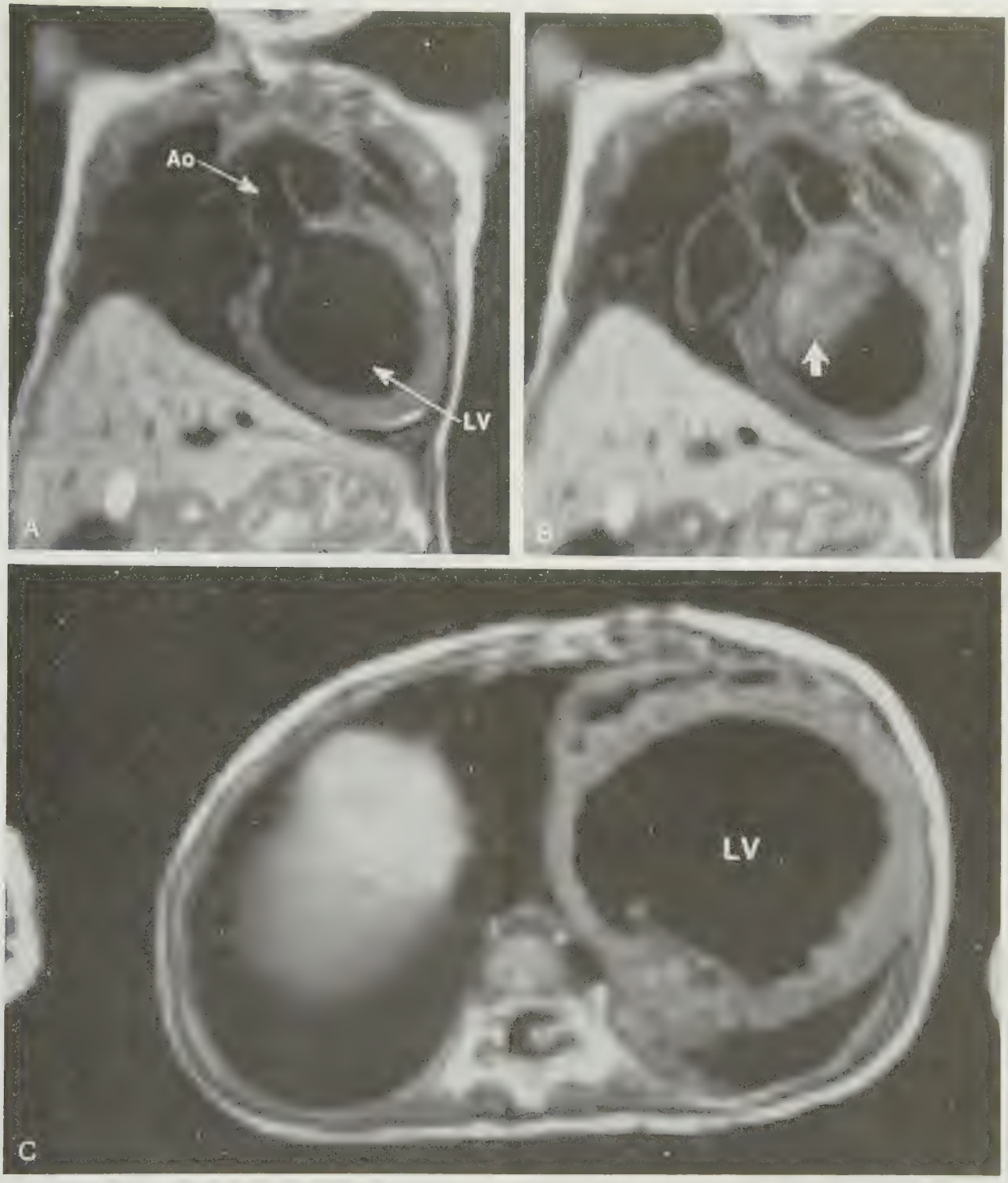

Fig. 51–20. Spin echo images obtained in a 7-yr-old patient with severe dilated cardiomyopathy. A. This paracoronal image was obtained with an echo time of 22 msec. The left ventricular cavity is severely dilated. B. This image was obtained in a paracoronal plane identical to the image in panel A but with an echo time of 15 msec. Note the increased signal intensity of the blood in the left ventricular outflow tract. Presumably, the shorter echo period results in reduced dephasing of spins across imaged voxels, and results in increased NMR signal intensity from theses voxels. Transverse spin echo image demonstrating the severe dilation of the left ventricular cavity in this patient in another plane. Ao = aorta; LV = left ventricle. (Orientation of panels A and B is as in Figure 51–2. Orientation of panel C is as in Figure 51–3.)

induced by acute infarction by showing contrast between normal and infarcted myocardium[86–88] (Fig. 51–21). The location and size of the infarct can then be assessed. Contrast agents, such as gadolinium diethylene triamine pentaacetic acid (DTPA) may facilitate the detection of injured and infarcted myocardium in the initial hours after coronary artery occlusion.[89–91]

Peripheral Atherosclerotic Vascular Disease

Because substantial contrast is generally demonstrated between the lumen and vessel walls by NMR imaging, peripheral arteries are often well visualized by NMR. Stenotic and aneurysmal areas can be clearly demonstrated in the larger vessels. Several experimental and clinical studies of NMR have demonstrated atherosclerotic plaques projecting into the lumen of larger peripheral arteries.[92–94] NMR has the potential for use in the evaluation of atherosclerotic vascular disease and its response to medical and surgical treatment. Current research, which is focused on the tissue-characterization ability of NMR, may make it possible to evaluate noninvasively the composition of the arteries and putative atherosclerotic plaques, and to determine such features as lipid and fibrous tissue content.[95]

Coronary Atherosclerosis

Although the coronary arteries are often visualized on NMR scans,[96,97] direct demonstration of the lesions of coronary atherosclerotic lesions is not possible with currently available NMR systems. Because they are small and move rapidly, coronary arteries are difficult to image. To demonstrate atherosclerotic plaques in these small vessels reliably, it will be necessary to achieve extremely high resolution and prevent motion artifact.

It is possible to determine the patency of aortocoronary bypass grafts with NMR imaging.[98,99] The use of surface coils can increase resolution and facilitate this determination.

Cardiac Functional Assessment by NMR

NMR shows much promise as a tool for cardiac functional assessment. Qualitative evaluation of overall ventricular function is easily made from systolic and diastolic short-axis, long-axis, or four-chamber images (Figs. 51–22 and 51–23). Left and right ventricular ejection fractions can be calculated from sets of systolic and diastolic images, using either Simson's rule or simplified modifications of it.[100,101] Ventricular ejection fractions determined by NMR have correlated well with ventricular ejection fractions determined by other techniques. Regional cardiac wall motion abnormalities can be evaluated either with a multislice rotation method employing spin echo sequences, or with the new cine NMR techniques.[102,103] The spin echo technique generally gives superior myocardial definition; however, the cine studies yield much better time resolution for an equivalent imaging period, and usually have adequate spatial resolution (particularly when implemented with velocity-compensation gradients).

Techniques of Clinical NMR

Optimization of Cardiovascular NMR Images

The quality of cardiovascular NMR images is determined by multiple parameters, some intrinsic to the subject studied and some determined by the NMR imaging system or its operator. A major factor in determining image quality is the signal-to-noise ratio, which is generally increased by increasing field strength. The relation between signal-to-noise ratio and field strength is complex, but seems to be linear at high field strength, where noise from the subject is the predominant form of noise, a situation that is gen-

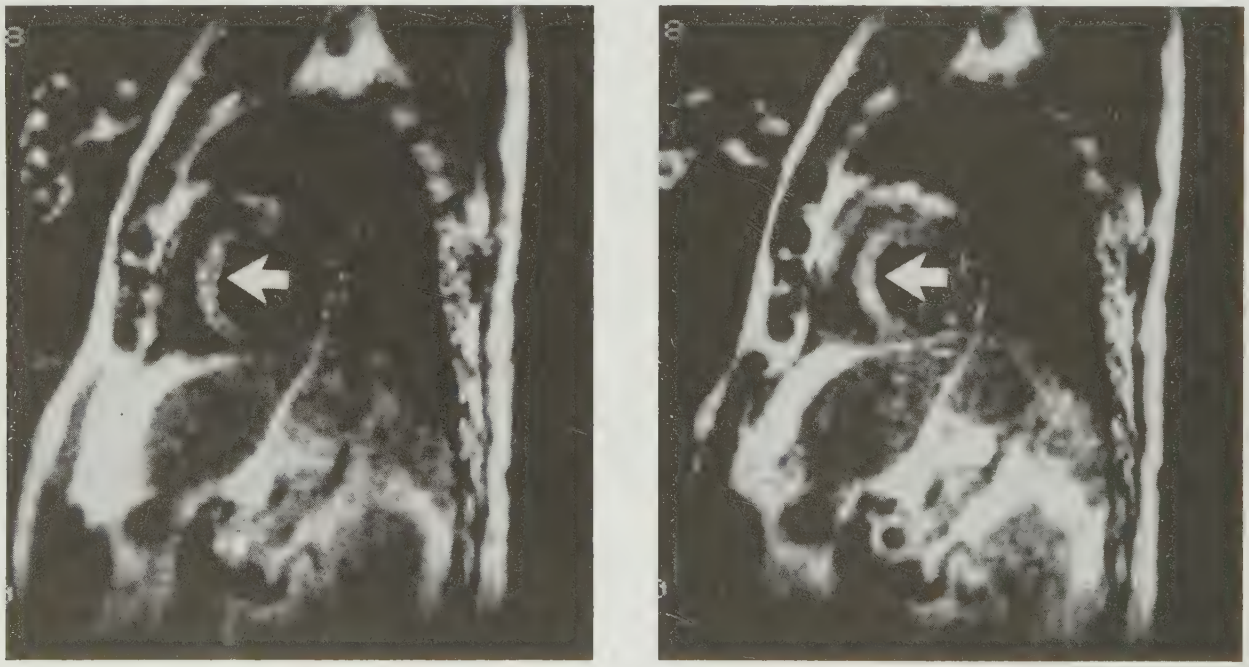

Fig. 51–21. Diastolic (left) and systolic (right) spin echo NMR images in patient with anteroseptal myocardial infarction. Note the increased signal intensity in the anteroseptal region of the left ventricle in comparison with other locations in the left ventricle (arrows). Note also that the contrast between the anteroseptal region and other regions of the ventricle is greater in systole than in diastole. (Orientation is as in Figure 51–4.)

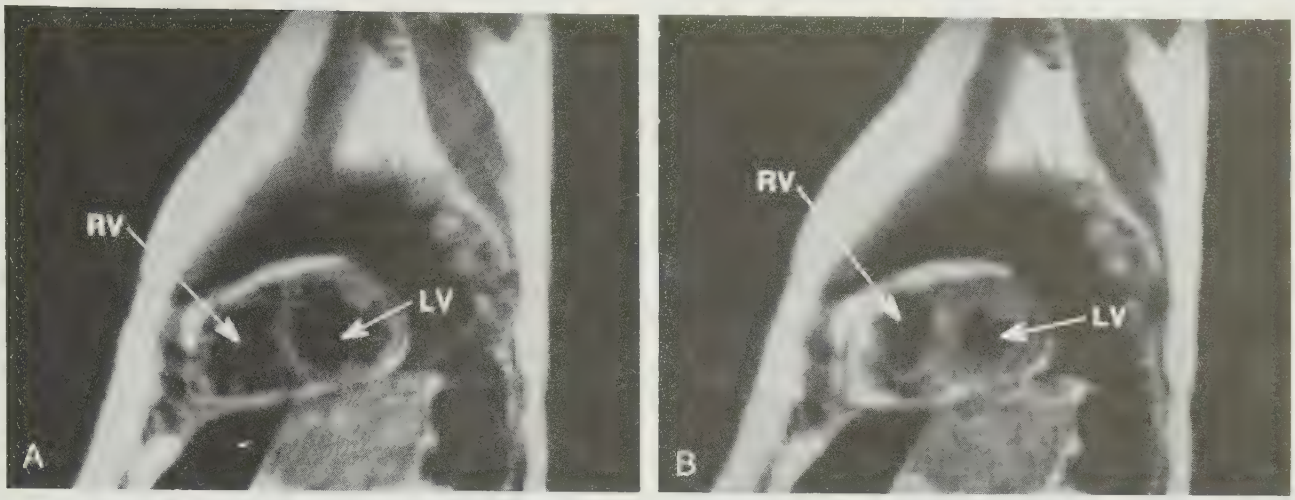

Fig. 51–22. Spin echo parasagittal images obtained in diastole (A) and systole (B) in short-axis sections at the midventricular level. RV = right ventricle; LV = left ventricle. (Orientation is as in Figure 51–4.)

erally prevalent in clinical imaging.[104] The signal-to-noise ratio may be increased by averaging, since signal increases linearly with the number of averages, while noise increases as the square root of the number of averages. Averaging, of course, will extend the time of NMR studies.

Image artifact due to subject motion can substantially degrade NMR images. Motion artifacts can be reduced with the techniques described in Chapter 7. Artifacts due to the presence of metals or other ferromagnetic substances may degrade NMR images. Careful screening of patients before examination is essential in order to prevent such objects from being inadvertently carried into the imager.

The diagnostic utility of NMR images is dependent in large part on the contrast-to-noise ratio between structures of interest. This contrast-to-noise ratio (C/N) is defined as the absolute value of the signal-intensity difference between two structures divided by the square root of the sum of the squared standard deviations of the signal intensities of the two structures[105]:

$$C/N = |SI_A - SI_B|/\sqrt{(\sigma^2{}_A + \sigma^2{}_B)}$$

where SI_A and SI_B indicate the signal intensity in region A and region B, respectively (this formula assumes no cross-correlation in noise between the regions of interest), and where $\sigma^2{}_A$ and $\sigma^2{}_B$ indicate the squares of the standard deviation of signal intensity in regions A and B, respectively.

Contrast can be maximized or minimized by appropriate manipulation of NMR imaging parameters. It is imperative that individuals interpreting NMR studies understand the underlying principles responsible for NMR image contrast. It is particularly important that interpreters of these studies realize that changes in the types of imaging sequences or in their parameters can result in major changes in the appearance of the resultant images without

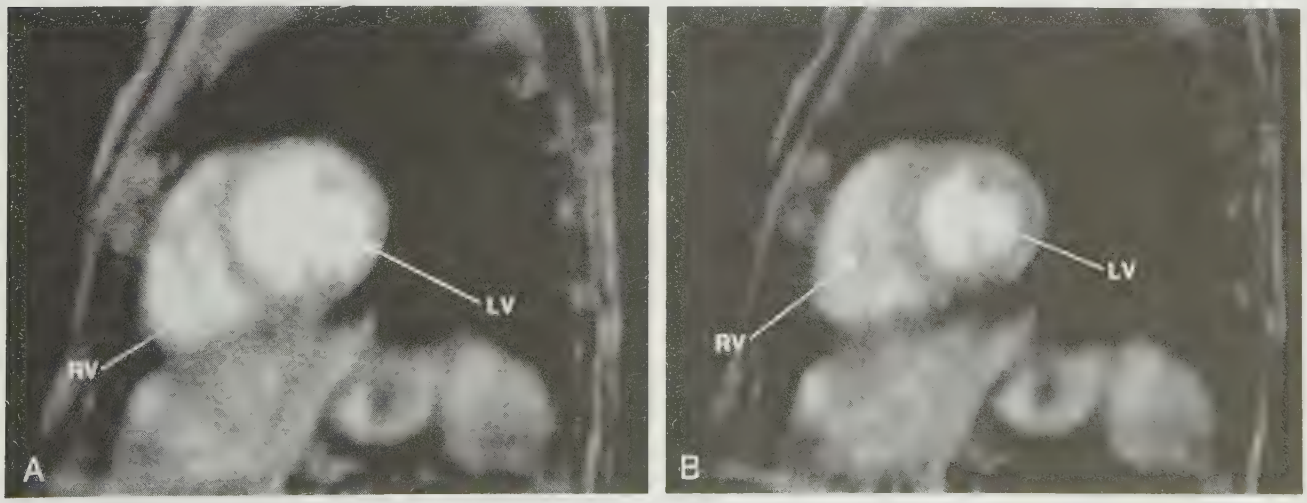

Fig. 51–23. Velocity-compensated FISP (fast imaging with steady precession) parasagittal images obtained in diastole (A) and systole (B) in short-axis sections at the midventricular level. RV = right ventricle; LV = left ventricle. (Orientation is as in Figure 51–4.)

any concomitant change in the imaged subject. Otherwise, the potential for misinterpretation is high.

The contrast between two regions of interest is, in general, a complex function of T1, T2, spin density, and blood flow with any given imaging sequence. Because of these multiple factors, we will consider the effect of these parameters on two commonly used imaging sequences, spin echo and FISP (fast imaging with steady precession).

The standard spin echo sequence, which employs a 90-degree initial excitation radiofrequency pulse, is versatile and can be used to emphasize T1, T2, spin density, or blood flow differences between regions of interest. Although images reflecting only the T1, T2, or spin density parameters can be produced by mathematical combination of sets of spin echo images, it is generally impractical to generate such images for routine clinical use. Furthermore, the quality of these images is degraded by the combination process. Rather, it is more effective in most clinical imaging to generate images that are "weighted" to reflect primarily T1, T2, spin density, or flow differences.[106]

T1 differences may be accentuated by appropriate choice of repetition time (TR) (see Chapter 37) (Fig. 51–24). To provide good delineation of T1 differences, it is necessary to use echo time (TE) (see Chapter 37) values substantially shorter than the T2 values of the tissues of interest. Until recently, most scanners were incapable of employing spin echo sequences with an echo time short enough to adequately detect T1 differences in the myocardium.[107,108]

T2 differences can be emphasized by proper selection of TE (Fig. 51–25). Because of T2 and T2* (effective transverse relaxation time) decay, the signal obtained from sequences with a long TE is often low. Thus the signal-to-noise ratio on images obtained with relatively long TE values is often reduced and image quality suffers.

Spin density differences are accentuated by a long TR and a short TE. Because of the requirement for a long TR, spin-density weighted images usually require a lengthy imaging time.

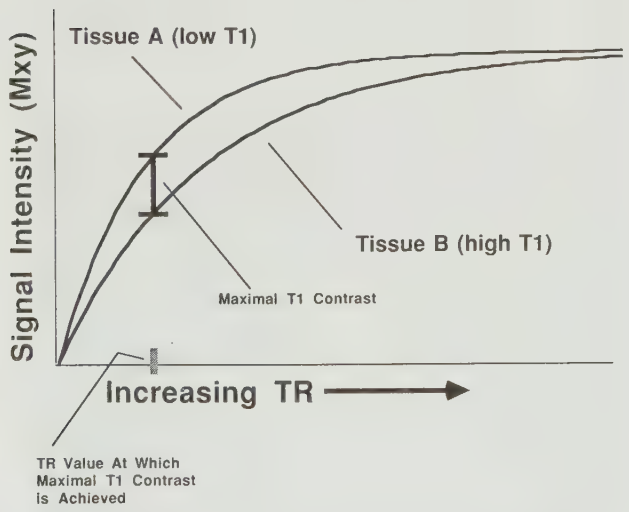

Fig. 51–24. If the T1 values of tissues of interest are known (even approximately), repetition time can be adjusted to emphasize T1 contrast differences between the tissues of interest. Unfortunately, cardiac synchronization of data acquisition interferes with this optimization, since repetition time is limited to multiples of the cardiac cycle with standard spin echo sequences.

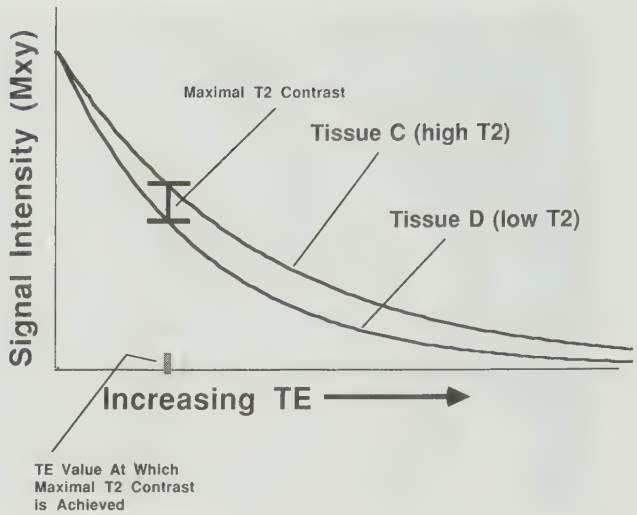

Fig. 51–25. The T2 contrast between two tissues of interest can be maximized by varying echo time. It should be noted, however, that the NMR signal obtained from any given tissue progressively decreases with increasing echo time.

In general, regions with relatively short T1 values in relation to TR tend to appear bright on spin echo images, and regions with relatively long T1 values in relation to TR will appear dark. Regions with relatively short T2 values in relation to TE appear dark and regions with relatively long T2 values in relation to TE will appear bright. Regions with a high spin density appear bright and regions with a low spin density will appear dark.[109]

Rapidly flowing blood has a very low signal intensity on spin echo images because substantial dephasing of nuclei occurs during the TE period. Therefore contrast between vessel walls and rapidly flowing blood or between myocardium and rapidly flowing blood is generally readily apparent. Stagnant or slowly flowing blood will appear brighter than myocardium or vessel wall in many cases because of the relatively long T2 of blood in relation to myocardium, and because of the slice entry phenomenon created by slowly flowing blood. Blood flowing at moderate velocities may appear bright if TE is made very short.

Weighting of imaging parameters to emphasize T1, T2, spin density, or blood flow differences can also be accomplished with FISP and other rapid imaging sequences. These techniques allow manipulation of the pulse flip angle α in addition to TR and TE. Since these sequences are primarily used for obtaining cine NMR studies, it is generally better to keep TR as short as possible so that more images can be obtained in a given interval and time resolution can be maximized.

T1 weighting with FISP is accomplished by increasing α to the 45- to 90-degree range. An increase in TR will accomplish additional T1 weighting. T2 or T2* weighting is produced with short TR values and with α in the 30- to 60-degree range. Spin-density weighting is best produced with a short TE and a low value of α. The signal intensity of flowing blood will be bright in relation to myocardium and vessel walls on most FISP images, because the NMR-sensitive nuclei in stationary structures become relatively saturated during the imaging sequence. Exceptions occur in the

case of extremely rapid blood flow, such as that produced by a stenotic cardiac valve. Blood in these regions of extremely rapid flow may appear dark. The signal intensity of flowing blood can be increased by shortening TE.[110,111]

Dynamic Cardiac NMR Imaging

Functional cardiac evaluation requires excellent time resolution. Rapid acquisition of cardiac NMR images can "freeze" the cardiovascular structures and facilitate such evaluation. Until recently, technical difficulties precluded application of these "real-time" techniques to patients of adult size. Furthermore, image quality was often unsatisfactory with early methods of this type. Newly introduced techniques make it possible to acquire complete NMR images of adequate quality in periods as short as 40 msec. Wider application of these techniques promises to facilitate cardiovascular NMR evaluation greatly.[112]

Another approach, which has achieved considerable success, is to acquire cardiac images from multiple time periods during the cardiac cycle with a standard multislice spin echo imaging sequence, with the acquisition time of each section synchronized to a different point in the cardiac cycle.[113,114] Once acquired, these images can be displayed in a video loop. With standard multislice spin echo imaging sequences, the order of anatomic slice selection can be changed in a rotational manner over several acquisitions. This process is known as multislice rotation and will yield images at different parts of the cardiac cycle in several tomographic sections. This method generally produces superior image quality and is a good technique for evaluation of overall ventricular function. However, its time resolution is limited in practical clinical settings, since only one image per tomographic section is created for each acquisition. Five acquisitions, each requiring 128 or 256 heart beats, would thus produce images at only five different points in the cardiac cycle—an inadequate number for wall motion studies. To produce images at 12 points in the cardiac cycle—probably the minimum acceptable number for wall motion studies—would require 12 acquisitions, which would be impractical clinically from a time standpoint. Modifications of this technique show promise for increasing time resolution. If two spin echo images per slice are obtained with each acquisition, time resolution can be doubled. Time resolution can be doubled again if half-Fourier acquisition is employed.

The new rapid imaging gradient echo sequences such as "FISP" (fast imaging with steady precession), "GRASS" (gradient recalled acquisition in the steady state), and "FLASH" (fast low-angle shot) have greatly facilitated dynamic cardiac imaging. With these techniques, TR can be made as short as 20 msec.[115–119] With such short TR periods, NMR data can be acquired at multiple points during each cardiac cycle. Of course, many NMR data acquisitions are necessary to produce an image. If the process is continued over many (usually 128 or 256) cardiac cycles, separate images can be built up from data obtained at each point of acquisition during the cardiac cycle. These images can be obtained in several tomographic sections orthogonal to the intrinsic cardiac axes. They can be displayed in cine loop format so that cardiac wall motion and blood flow patterns are more easily appreciated. With these methods a complete functional evaluation of the heart can be obtained in only a few minutes (Fig. 51–26).

Flowing blood usually has a higher signal intensity than myocardium on images produced by short TR gradient echo sequences. This effect occurs because the myocardium in a given slice becomes relatively saturated by the repetitive radiofrequency pulses of the short TR sequences, whereas the flowing blood in the slice is constantly being replaced by fresh, unexcited nuclei. Hence, the blood produces a stronger NMR signal than the myocardium in most cases (Figs. 51–27 to 51–29). However, when blood flow is turbulent, there will be a relatively large distribution of velocities across voxels of blood. Under the influence of magnetic field gradients the nuclei within these voxels will accumulate substantial phase differences. These phase differences will diminish the NMR signal produced from the voxel. It follows that the signal intensity of regions of turbulently flowing blood will be low.

Since moving blood usually has a high signal intensity on gradient echo sequences, spatially misregistered signal caused by motion of this blood along magnetic field gradients will also have high signal intensity. The high intensity of this spatially misregistered signal can substantially degrade images. By contrast, spatially misregistered signal from flowing blood imaged with a spin echo technique will have a low signal intensity and is less noticeable. Gradient moment nulling rephases moving spins at the echo and thus reduces the effect of spatial misregistration in gradient echo sequences. Image quality is often substantially enhanced by this process.

NMR Angiography

Since flowing blood has NMR characteristics that differ from stationary tissues, it is possible to produce NMR images that demonstrate regions containing flowing blood as areas of high signal intensity against a dark background, in a manner similar to angiography.[38] There are several techniques for producing these "NMR angiograms." The method that has achieved the most widespread application is that of subtraction arteriography.[120] Two electrocardiographically synchronized images are produced with a different delay, and the resulting images are subtracted. The delay is chosen so that one image will be obtained in diastole and another near peak systole. The diastolic image will show increased signal intensity in the lumen of arterial vessels, as the blood will be essentially stationary. The systolic image will show decreased signal intensity in the lumens of these vessels, as the NMR signal will be dephased by the rapidly flowing blood. The image obtained by subtracting the systolic from the diastolic image will depict the functional arterial tree. If the selection slice is made thick, a projective image will be produced with a striking resemblance to an arteriogram.

The original subtraction arteriography method is susceptible to misregistration artifacts when motion occurs between the time the systolic image is acquired and the time the diastolic image is acquired. Data acquisition during multiple phases of the cardiac cycle with a rapid imaging gradient technique can eliminate a substantial amount of misregistration artifact since systolic and diastolic images are then acquired over the same set of cardiac cycles.

A further modification of the subtraction arteriographic method employs a phenomenon known as gradient refocusing.[121–123] In the standard spin echo pulse sequence, the gradient in the frequency-encoding direction is turned on during the time of data acquisition from the spin echo and prior to the 180-degree pulse. Stationary NMR-sensitive nuclei are rephased by this gradient, but moving NMR-sensitive nuclei exhibit velocity-sensitive dephasing. If ad-

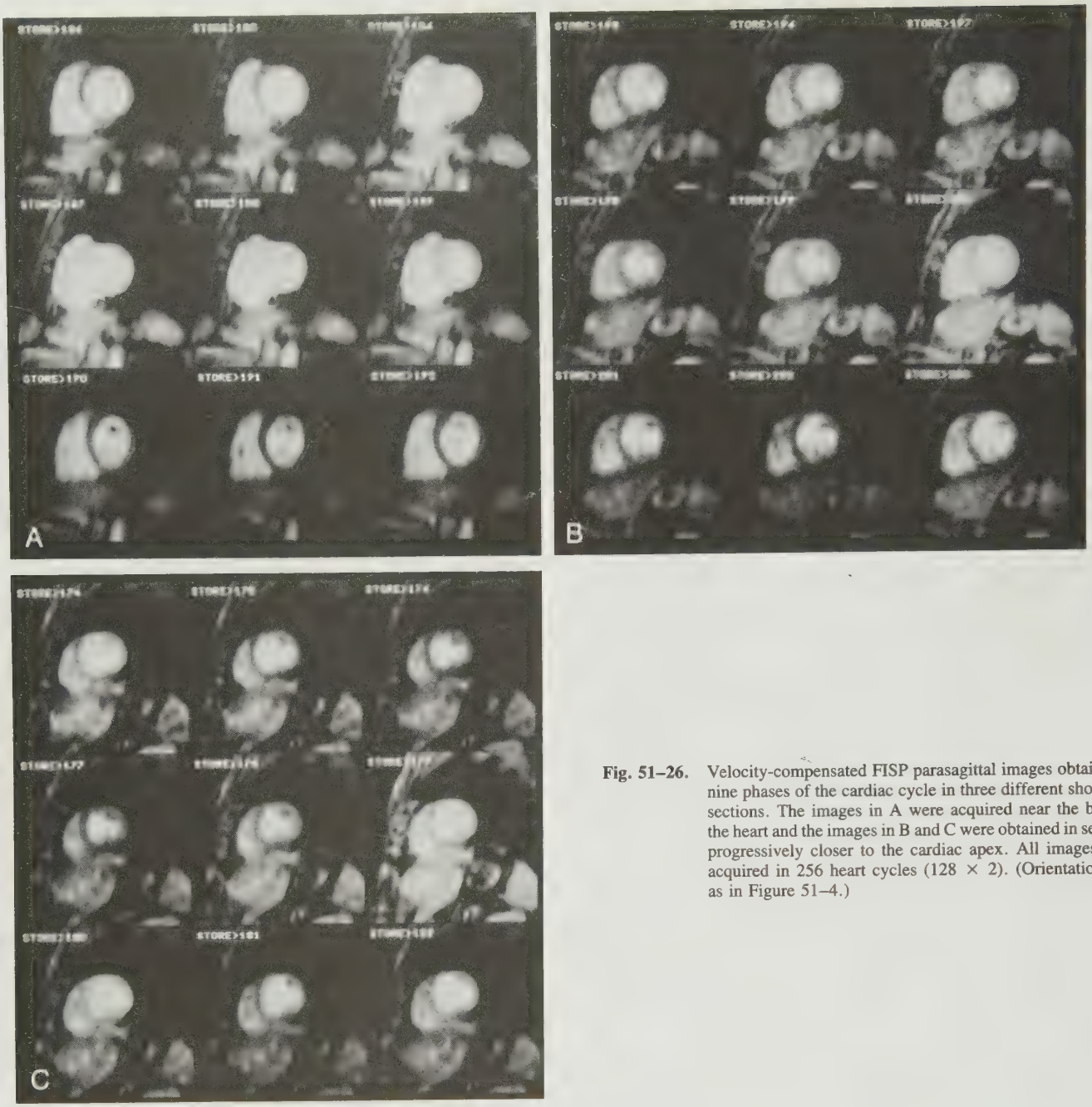

Fig. 51–26. Velocity-compensated FISP parasagittal images obtained in nine phases of the cardiac cycle in three different short-axis sections. The images in A were acquired near the base of the heart and the images in B and C were obtained in sections progressively closer to the cardiac apex. All images were acquired in 256 heart cycles (128 × 2). (Orientations are as in Figure 51–4.)

ditional magnetic field gradients are applied in the frequency-encoding direction in a bipolar (having equal amplitude and opposite direction) fashion, nuclei with constant velocity can be refocused so that they are in phase at the time of the echo, and give substantial NMR signal. Magnetic field gradients can also be added to an imaging sequence in such a manner that dephasing of moving nuclei is strongly accentuated. Subtraction of images generated with dephasing gradients from images generated with rephasing gradients yields an image of the flowing blood. Dephasing and rephasing of gradients can be incorporated into the gradient echo rapid-imaging pulse sequences to decrease acquisition time or to increase the number of phases in the cardiac cycle obtained when the acquisition is synchronized to the electrocardiogram. Acceleration rephasing and defocusing gradients can be added to these sequences. Arterial flow can be distinguished from venous flow with these acceleration-sensitive sequences.

Another method for generating a representation of flow with NMR imaging is the phase display. The NMR imaging process yields a quantitative estimate of the value of the transverse component of the net magnetization vector of the imaged voxels of the subject. This quantity is a complex number with both magnitude and phase. Most NMR images are constructed strictly from magnitude information. However, a separate image derived from the phases of the imaged voxels can also be constructed. This is done by establishing a correspondence between the gray scale of the image and the phase change of the voxels. The zero-degree

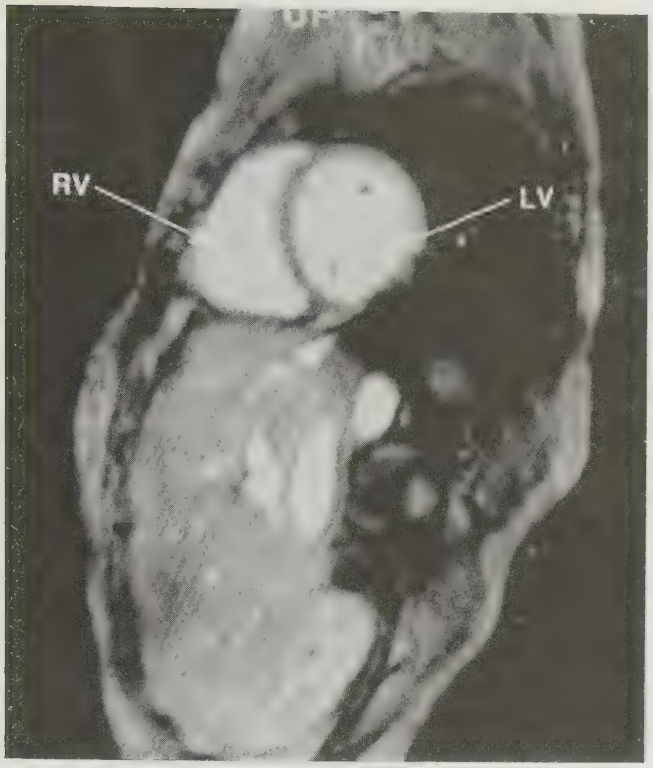

Fig. 51–27. Parasagittal image obtained in a short-axis section near the base of the heart with a velocity-compensated FISP sequence. Note that the blood in the ventricular chambers and blood vessels has a high signal intensity relative to the myocardium and the blood vessel walls, a feature characteristic of these short TR sequences. RV = right ventricle; LV = left ventricle. (Orientation is as in Figure 51–4.)

phase change of the stationary protons is generally set to the midrange of the gray scale, with phase changes of +180 degrees and −180 degrees at the highest and lowest intensities, respectively. Gray scale reversal will occur if the phase change exceeds 180 degrees from the reference phase. Flow and motion manifest themselves as abrupt changes in the signal intensity of the phase images. Phase images are obtainable with many NMR systems in a straightforward manner, and are particularly useful in facilitating the distinction of slow flow from thrombus.[124,125]

Van Wedeen has devised a method for NMR flow densitometry with projective angiography. With this technique, which requires radiofrequency pulses of sufficient bandwidth to affect all protons within the field of view, the phase of the magnetization vector of a moving proton is proportional to its velocity of flow, and the resultant signal intensity of the projective image of the vessel is proportional to the volume of flow through it.[126]

A great advantage of contrast angiography is that selective injections can be made. Selective injection facilitates demonstration of vessels that overlie other vessels or the cardiac chambers. Dixon and colleagues described a method of NMR angiography that is a step toward selective NMR angiography.[127] They employed the principle of adiabatic fast passage, which reverses the magnetization of moving spins, to label blood passing through the field of a surface coil placed on the necks of human subjects. The technique enabled them to visualize the common, internal, and carotid arteries in a projective format.

Chemical Shift Imaging

Two major types of protons contribute to the NMR signal generated by biologic subjects. These are water protons and protons linked to aliphatic carbons. The two types of protons resonate at slightly different frequencies. Dixon developed a novel method to generate images principally from water protons and images derived principally from water protons.[128] This chemical shift imaging method is based on the principle that the centerpoint of a refocused gradient echo can be moved so that the net magnetization vectors of aliphatic and water protons point in opposite directions at the time of data acquisition and therefore tend to cancel.[129] An out-of-phase proton image is formed with this centerpoint shift, and another, in-phase, image is formed. When the images are added, a water image is formed. When the out-of-phase image is substracted from the in-phase image, a fat image is formed. The advantage of this form of imaging is that fat content, rather than T1 or T2 relaxation times, becomes the major source of imaging contrast. The Dixon technique has shown promise as a method for detecting fatty infiltration of the liver.[130] It also may be useful for evaluation of lipomatous tumors of the heart and distinguishing epicardial fat from infiltrative disorders in the paracardiac region. Modifications of this method may prove useful for evaluating arterial vessels for signs of atherosclerosis.

Since the original Dixon method depends on subtraction or addition of images from two different acquisitions, the technique is subject to the effect of misregistration artifacts that may occur because of patient movement during the two acquisitions. Recently developed methods have made it possible to reduce such artifacts by acquiring multiple lines or even entire images subsequent to a single excitation.[131]

Electrocardiographic Synchronization

Synchronization of NMR data acquisition to the cardiac cycle is usually necessary to reduce motion artifact and obtain useful images of cardiovascular structures.[132] The most convenient way to accomplish synchronization with the cardiac cycle is to initiate data acquisition in conjunction with the electrocardiogram[133,134]—a process that is not truly "gating," but rather, synchronization of data acquisition to the cardiac cycle.[135]

Several important technical considerations must be addressed if technically adequate synchronization of the NMR data acquisition is to be achieved. First, the rapidly changing magnetic field gradients will induce electrical currents in the electrocardiographic leads, thereby creating artifacts. These artifacts may confuse the electronic triggering mechanism, causing it to initiate data acquisition at undesirable times. These artifacts also may obscure the electrocardiographic signal, so that the ST segment and other portions cannot be seen. The effectiveness of the electrocardiogram as a tool for monitoring acutely ill patients is thus reduced.

In order to avoid imaging artifacts, electrocardiographic electrodes and leads should be made from nonparamagnetic materials. The artifacts in the electrocardiographic signal may be further reduced by wrapping the leads and placing the electrodes near each other, to reduce the size of the current loops created by the monitoring system.[136,137] In addition, an electrocardiographic monitoring and synchronization device with improved capabilities has

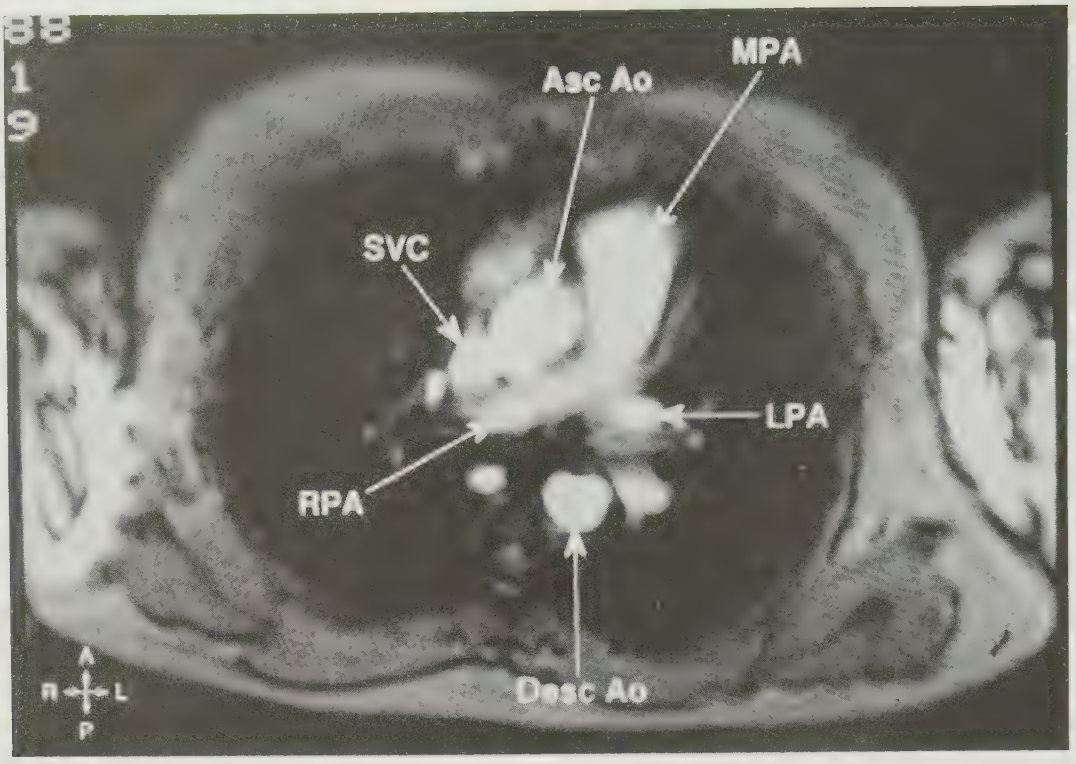

Fig. 51–28. Velocity-compensated FISP paratransverse image obtained in a plane lying along the right ventricular outflow tract to simulate a view analogous to the angiographic "sitting-up view." Asc Ao = ascending aorta; Desc Ao = descending aorta; MPA = main pulmonary artery; LPA = left pulmonary artery; RPA = right pulmonary artery; SVC = superior vena cava; A = anterior; P = posterior; L = left; R = right.

Fig. 51–29. Velocity-compensated FISP transverse images obtained in different phases of the cardiac cycle at 25-msec intervals at the level of the pulmonary artery bifurcation. Sixteen images are shown. Twenty images were acquired in 256 heart cycles (128 × 2). (Orientations are as in Figure 51–3.)

recently been introduced to facilitate active reduction of these artifacts.[138] This device also facilitates identification of abnormalities of cardiac rhythm during NMR studies, and thus improves patient monitoring capabilities. The device employs a time-varying low-pass filter. It takes advantage of the time-varying nature of frequency content of the electrocardiographic signal. The high-frequency components of the electrocardiographic signal are generally contained in the QRS complex. The remainder of the electrocardiogram contains primarily low-frequency components. The gradient artifacts in the electrocardiographic signal are essentially entirely of high frequency. Since the magnetic field gradients are triggered by the QRS complex, and in general are not activated until after the completion of the QRS complex, it is possible to activate the low-pass filter after the QRS complex, and before the effect of the gradients appears in the electrocardiographic signal. An electrocardiographic signal of good quality is thus obtained during NMR data acquisition. Cardiac synchronization of NMR data acquisition may be hindered by arrhythmias. When the irregularities are only occasional it is possible to avoid data acquisition during the time of the irregular beats with proper setting of the filter durations.

Enhancement of NMR Contrast with Paramagnetic Agents

Contrast between different tissues can be accentuated by appropriate choice of NMR imaging pulse sequence parameters, as noted above. Sometimes, however, the spin density, T1 and T2 relaxation times, and motional characteristics of two different types of tissue are so similar that they cannot be clearly distinguished by pulse sequence manipulation. Examples of two such

tissues are normal and injured cardiac muscle in the first hours after coronary occlusion. Several investigators have demonstrated that a paramagnetic ionic form of gadolinium, a rare earth element, can accentuate the contrast between normal and injured myocardium after intravenous injection.[139–142] Because gadolinium is toxic in its free ionic form, it is complexed with diethylene triamine pentaacetic acid (DTPA), a chelating agent. Like most paramagnetic agents, gadolinium-DTPA shortens both T1 and T2, with the more substantial shortening occurring in T1.[143–145] When given after complete coronary occlusion, it modifies the NMR relaxation characteristics of the normally perfused myocardium. When T2-weighted pulse sequences are employed, the normal myocardium will appear dark in relation to the injured myocardium. Greater degrees of T2 weighting are associated with greater contrast between normal and injured myocardium. Conversely, heavily T1-weighted sequences will cause images of normal myocardium to have increased signal intensity in comparison with images of injured myocardial tissue. Recent evidence suggests that when gadolinium-DTPA is given after complete coronary occlusion, the area of infarction is defined, as opposed to the entire region at risk for infarction.[146]

Clinical Cardiac NMR Spectroscopy

Studies of the human myocardium with NMR spectroscopy are just beginning. A great deal of technical development will be necessary before NMR spectroscopy can be routinely applied in a clinical setting. Whitman and colleagues[147] performed ^{31}P NMR spectroscopy with a surface coil placed directly over the sternum in an 8-mo-old female infant with a congenital cardiomyopathy of uncertain cause. No attempt at spatial localization of signal was made, but it was noted that the patient had massive cardiomegaly with minimal skeletal muscle development, so that the contribution of skeletal muscle to the cardiac nuclear magnetic resonance signal was presumably minimal. The infant's myocardial creatine-to-inorganic-phosphate ratio was determined and was found to be half that found in a normal control infant. Intravenous and oral glucose were administered. This treatment raised the myocardial creatine-to-inorganic-phosphate ratio from 1.0 to 1.8 without affecting this ratio in skeletal muscle. Medium-chain triglycerides had no noticeable effect on myocardial metabolism.

Rajagopalan and colleagues[148] studied six normal subjects and six patients with hypertrophic cardiomyopathy with ^{31}P NMR spectroscopy. Rotating frame zeumatography (see Chapter 37) was employed for spatial localization. Because of technical limitations on the depth of sampling, spectra were apparently obtained primarily from the right ventricular free wall. The normal subjects were determined to have a creatine-to-ATP ratio of 1.53 ± 0.12. One patient with severe right ventricular hypertrophy and a history of cardiac decompensation had a creatine-to-ATP ratio of 0.9 ± 0.2 as determined on three separate occasions. The remaining patients, who did not have right ventricular hypertrophy (though all had substantial interventricular septal and/or left ventricular free wall hypertrophy) had myocardial creatine-to-ATP ratios within the normal range.

Bottomley and Andrew[149] employed ^{31}P NMR spectroscopy to evaluate seven normal control subjects and four patients with confirmed acute anterior myocardial infarction 5 to 9 days after the onset of symptoms. Spatial localization of signal was performed with a surface coil in conjunction with the DRESS (depth-resolved surface-coil spectroscopy) technique. Proton spectroscopic imaging was employed to localize endocardial, epicardial, or transmural regions of interest. Substantial reductions in the endocardial creatine-to-inorganic-phosphate ratio were noted in the patients in comparison with controls.

Hazards of and Contraindications to NMR

Standard clinical imaging magnets present no known hazards to biologic materials. Three different magnetic fields are employed by such magnets. These are 1) the relatively large static mangetic field, 2) smaller, but rapidly varying magnetic fields secondary to the magnetic field gradients, and 3) radiofrequency pulses. Guidelines set by the Food and Drug Administration keep the strength of these fields well below levels that could cause significant biologic effects.[150–153] Animal studies evaluating the influence of static magnetic fields have not demonstrated significant bioeffects for fields of up to 2 Tesla. Chinese hamster cells and human lymphocytes incurred no cytogenetic damage in a study exposing them to moderate and high static magnetic field strengths and to prolonged stimulation with time-varying magnetic field gradients and radiofrequency pulses. The amount of radiofrequency power deposition that these cells were subjected to was far in excess of that given during clinical imaging studies.[153] Thousands of patients have undergone NMR studies without any noticeable immediate or longterm sequelae. Because these magnets do attract ferromagnetic objects, extreme caution should be employed in approaching magnets with objects containing iron or other ferromagnetic materials. It is best to keep an NMR magnet in a room from which such objects are barred. A number of unfortunate accidents have occurred because ferromagnetic objects (such as iron oxygen cylinders or wrenches) came too close to a magnet.

Implanted metallic objects are a subject of particular concern, since they could potentially undergo undesirable torquing movements if the magnetic field is sufficiently strong and if they contain sufficient ferromagnetic material. Fortunately, surgical clips and sternotomy wires (usually stainless steel) implanted in the chest and abdomen are often only weakly ferromagnetic. Furthermore, these devices quickly become immobilized by surrounding fibrous tissue. Patients with these implants can be routinely studied; however, the wires and clips may cause image artifact.

Intracranial aneurysm clips do not become immobilized by fibrous tissue, however, and can undergo torque in a magnetic field. Although nonferromagnetic aneurysm clips are now available, NMR studies of patients with these intracranial clips are contraindicated unless the clip is specifically known to be nonferromagnetic. Other types of intracranial ferromagnetic objects or materials may also contraindicate NMR studies. Welders are prone to accidents that may result in the intracranial implantation of ferromagnetic chips. One case has been reported in which a patient who had suffered such accidents sustained damage to his optic nerve.[154]

Prosthetic heart valves manufactured after 1964 contain little ferromagnetic material. Hence, patients with these valves in place can be routinely studied.[155] Heart valves manufactured before 1964 may contain substantial ferromagnetic material. Patients with these valves in place should be studied only if their valve type has been evaluated and found to exhibit acceptable torquing in a magnetic field of similar strength to the contemplated imaging field.

The presence of a cardiac pacemaker is a contraindication to

NMR studies, mainly because of concern that the pacemaker electronics might be damaged.[156] It is also possible that magnetic field gradients could induce currents in the pacemaker leads and that these currents could be recognized as cardiac activity by the electronic sensing mechanisms of the pacemaker. The pacemaker might then be improperly inhibited. Another possibility is that the reed switch of the pacemaker could be activated, causing it to pace in the asynchronous mode. There is a theoretical concern that current induced in pacing wires by the magnetic field gradients could actually cause electrical stimulation of the heart. Many patients have now been studied in whom temporary pacing wires were left in place after surgery, and amputated at the point of passage through the patient's skin. No abnormal effects have been observed in these studies, except for some image artifact.

Pregnancy is presently a relative contraindication to NMR studies, though the magnetic field levels used in clinical imagers have no known effects on the embryo, and though patients have undergone NMR imaging during all trimesters of pregnancy without reported ill effect on the mother, fetus, or infant. When maternal health considerations require diagnostic studies, NMR may be preferable to methods that employ roentgen rays, such as computed x-ray tomography or angiography.

Summary

Clinical NMR is a complex diagnostic tool that demands much of the examining physician. However, NMR promises to facilitate the diagnostic evaluation of congenital and acquired cardiovascular disease in many ways. Current NMR techniques can provide excellent anatomical and functional definition of many aspects of cardiovascular disease. NMR techniques being developed may greatly increase the clinician's ability to evaluate the cardiovascular system metabolically.

POSITRON EMISSION TOMOGRAPHY

Considerable experimental work has demonstrated that positron emission tomography (PET) has important potential applications in the evaluation of cardiovascular disease.[157,158] Clinical studies of this imaging method have primarily evaluated its efficacy in adult ischemic heart disease, but there are now several reports of the use of PET to assess patients with cardiomyopathy of various causes. PET can provide considerable information about regional myocardial perfusion and metabolism, within its inherent limitations of spatial and temporal resolution. Because of these limits, which particularly serve to reduce the quality of studies in patients with small hearts and rapid heart rates, cardiac PET scanning has not been widely applied in pediatric populations. As patients with congenital heart disease age, however, myocardial dysfunction becomes progressively more common. PET scanning may have an important role to play in the clinical evaluation of these older patients.

An Overview

PET scanning employs positron-emitting radionuclides. Positrons travel a short distance in tissue before colliding with an electron. The collision results in annihilation of both electron and positron, with the release of two 511-keV photons at approximately 180-degree angles. Since the photons are produced at the same instant, they will strike a surrounding detector ring simultaneously, except for a slight difference in time of flight dependent on the relative distance of the positron-electron collision from the center of the detector ring. With computer methods, it is possible to use the virtual coincidence of detection of the photon pair to assign the location of the positron-electron collision spatially in a relatively exact manner. The location of the original radionuclide producing the positron can then be inferred with a modest amount of ambiguity determined by the average distance that the positron travels prior to collision. The number of radionuclide particles present in each small region (voxel) of a tomographic plane defined by the detector ring is then estimated from the number of photons arising from the voxel, and a tomographic image is subsequently reconstructed from this estimate.[159] Carbon, oxygen, and nitrogen all have positron-emitting isotopes. Thus many biologic compounds of interest can be labeled and used as tracers.[160] Unfortunately, these isotopes have very short half-lives. Hence, an on-site cyclotron and organic synthesis laboratory is necessary to exploit such physiologic tracers. Rubidium-82, which can be produced with an on-site radionuclide generator, may be a more practical tracer for myocardial perfusion studies.

Clinical Studies in Ischemic Heart Disease

Identification of myocardial ischemia is a problem of major importance in diagnostic cardiology, and one that has become of particular concern in the past few years, with the introduction of methods for salvage of endangered myocardium. Ischemic tissue is at risk for damage, but potentially could resume its role as normally functioning myocardium if the hemodynamic cause for the ischemia were eliminated. When myocardium has suffered irreversible injury, however, aggressive intervention to relieve the causative coronary obstruction only exposes the patient to needless risk. It follows that the appropriateness of therapeutic decisions in patients with suspected ischemic heart disease depends, in many cases, directly upon the accuracy with which normal, ischemic, and irreversibly injured myocardial tissue can be identified and anatomically distinguished.

Quantitative blood-flow measurements are not feasible with single photon radionuclide methods because the variable attenuation of the photons produced by these radionuclides cannot be easily corrected for.[161] By contrast, the coincidence-detection method used by PET scanners facilitates determination of absolute tracer concentration, and makes quantitative blood-flow determination at least theoretically possible. The short half-life of the positron-emitting radionuclides employed facilitates sequential examination, which might be performed to follow the evolution of an episode of ischemia or infarction. Because resting coronary blood flow is decreased only when coronary artery narrowing is in excess of 85%, resting cardiac perfusion studies are insensitive for detection of coronary artery disease.[162] The presence and location of coronary disease can be inferred when characteristic regional perfusion abnormalities become apparent with exercise or after pharmacologic vasodilation with such agents as dipyridamole.

Radionuclide compounds that have been successfully employed for perfusion scanning with PET include ^{13}N ammonia, rubidium-82, and ^{15}O water. Each of these compounds has advantages and disadvantages as a perfusion tracer. ^{13}N ammonia, which must be produced by a cyclotron, has a physical half-life of 10 min, a first-pass retention or extraction factor in the myocardium of 80%, and a biologic half-life of over 1 hr.[163] ^{13}N ammonia exists in the blood

in equilibrium with the ammonium ion ($^{13}NH_4^+$). At physiologic pH, 95% of the tracer is in the ionic form. This ion is trapped within myocardial cells by the glutamine synthetase reaction. This reaction is energy dependent and operates at lower rates during acute myocardial ischemia and pH levels below 7.0. Thus decreased uptake of ^{13}N ammonia (and consequent underestimation of flow) is apparent under these conditions. Decreased uptake is also apparent at high flow rates (>2.5 ml/min/g). However, for most physiologic conditions, estimates of regional myocardial blood flow with ^{13}N ammonia appear to be reasonably accurate when properly corrected for tracer decay.

The myocardium extracts almost 100% of ^{15}O water on the first pass, and its uptake is not affected by metabolic factors. However, the short half-life (2 min) of this tracer, which must be produced in a cyclotron, creates technical difficulties, and the high concentration of ^{15}O water in the lungs and blood may necessitate subtraction of blood pool activity.[164] Blood-pool activity may be evaluated separately by PET imaging after administration of small quantities of ^{15}O carbon monoxide. Rubidium-82 also has a short half-life (76 sec) but can be produced by generator.[165] The extraction fraction of rubidium is only about 50%, and varies with metabolism and blood flow. This relatively low and variable extraction fraction complicates quantitative evaluation of myocardial blood flow with rubidium. However, promising results have been obtained in experimental animals with a tracer kinetic model, which enables correction for this variable extraction.

Qualitative analysis of PET perfusion scans has demonstrated good correlation of exercise-induced perfusion defects with regions of myocardium supplied by obstructed coronary arteries. Schelbert and colleagues examined 13 normal volunteers and 32 patients with angiographically documented coronary artery disease at rest and after dipyridamole treatment.[166] PET scans were performed with ^{13}N ammonia. The normal volunteers showed no perfusion deficits. In the patients, 52 of 58 coronary stenoses were correctly identified. All patients with double- and triple-vessel disease were correctly identified and 15 of 16 patients with single-vessel disease were correctly identified. In a subgroup of 19 patients, exercise planar thallium-201 perfusion studies were also performed. Planar thallium evaluation correctly identified the area of coronary artery stenosis in 11 of 19 cases. PET correctly identified the stenosis in 17 of 19 cases. The presence of coronary stenosis has also been identified with rubidium-82, and ^{15}O water.

Assessment of regional myocardial metabolism with PET has also been found helpful in patients with ischemic heart disease. When myocardial cellular glucose uptake mechanisms are functioning, ^{18}F deoxyglucose will be phosphorylated and trapped inside myocardial cells. Experimental evidence suggests that glucose uptake is preserved even in the presence of severe ischemia causing loss of regional contractility, provided cell damage is not irreversible.[167] Myocardial uptake of ^{13}N ammonia is decreased by such ischemia, as has been noted. Thus when both ^{13}N ammonia and ^{18}F deoxyglucose are administered, regions in which uptake of both tracers is depressed can be identified as irreversibly injured, and regions in which only ^{13}N ammonia uptake is decreased can be identified as ischemic but potentially salvageable myocardium. Using this method of evaluation, Tillisch and colleagues studied 17 patients who had preoperative abnormalities of left ventricular wall motion.[168] They predicted that wall-motion abnormalities in regions of preserved ^{18}F deoxyglucose uptake but depressed ^{13}N ammonia uptake would be reversible by coronary bypass surgery and that wall-motion abnormalities in regions where both isotopes was depressed would not be reversible. Wall motion was evaluated by radionuclide or contrast angiography or both. Reversibility was correctly predicted in 35 of 41 myocardial segments and irreversibility in 24 of 26 segments. By contrast, electrocardiographic evidence of irreversibility (presence of a pathologic Q wave attributable to a hypokinetic myocardial segment) was relatively inaccurate in predicting the return of contractile function. Studies performed with this double-tracer technique in patients with acute and chronic myocardial infarction suggested the presence of persistently hypoperfused but viable regions of myocardium that were not apparent by electrocardiography or gated-wall-motion radionuclide studies.

Myocardial free fatty acid and uptake and metabolism is depressed by ischemia. Thus ^{11}C palmitate can be used as a tracer for evaluation of the extent of myocardial ischemia and its response to treatment. Sobel and colleagues performed PET studies with ^{11}C palmitate in 19 patients with the diagnosis of transmural myocardial infarction upon hospital admission and again 48 to 72 hr after intracoronary administration of tissue-type plasminogen activator or streptokinase.[169] Thrombolysis occurred in 11 of the patients. The regions of coronary occlusion were apparent as perfusion defects on the initial PET scans. In each instance angiographic evidence of coronary reperfusion was accompanied by improvement in the uptake of ^{11}C palmitate in the jeopardized region. Interestingly, myocardial wall-motion abnormalities often did not immediately improve in the reperfused areas. Thrombolysis did not occur in 8 patients, and there was no improvement in the PET studies of these patients.

Normal subjects exhibit a homogeneous uptake of ^{11}C palmitate. The clearance of ^{11}C palmitate from the myocardium occurs in a biexponential fashion. The rapid first phase of clearance is determined by the rate and amount of ^{11}C-labeled carbon dioxide release caused by the oxidation of the palmitate. The second, and slower, phase is thought to be determined by incorporation of ^{11}C into the endogenous lipid pool. Grover-McKay and colleagues studied 10 patients at rest and during atrial pacing with ^{11}C palmitate PET.[170] During the pacing, it was noted that ^{11}C clearance half-times were 17% longer and residual fractions 14% higher in normal myocardium than in myocardium at risk. The findings were interpreted as suggesting that metabolic reserve for free fatty acid oxidation is impaired in myocardium supplied by stenotic coronary arteries.

Clinical Studies in Cardiomyopathy

Several reports have documented abnormalities in cardiac PET studies of patients with cardiomyopathy. Geltman and colleagues studied 13 normal subjects, 17 patients with congestive cardiomyopathy, and 6 patients with transmural myocardial infarction with ^{11}C palmitate PET scans.[171] Studies obtained from the normal subjects demonstrated homogeneous accumulation of ^{11}C palmitate within the myocardium. Studies of patients with transmural myocardial infarction were characterized by discrete regions of depressed accumulation of the tracer, corresponding to the region of infarction, surrounded by regions of homogeneous tracer uptake in the residual normal myocardium. The studies obtained from patients with cardiomyopathy, however, demonstrated substantial spatial heterogeneity of tracer distribution throughout the entire myocardium. This spatial heterogeneity correlates with patholog-

ical findings in patients with congestive cardiomyopathy demonstrating the presence of patchy and variable fibrosis and with histochemical evaluations suggesting patchy metabolic derangements, including depression of oxidative phosphorylation. It was suggested that spatial heterogeneity of ^{11}C palmitate uptake might prove to be a useful tool for early detection and characterization of cardiomyopathy.

Schelbert and colleagues investigated the metabolism of ^{11}C palmitate with PET in 5 normal volunteers and 16 patients with ventricular dysfunction, including idiopathic dilated cardiomyopathy, and cardiomyopathies secondary to doxorubicin (Adriamycin) cardiotoxicity, sickle cell anemia, myocarditis, hypertension, and ischemia.[172] Subjects were studied after an overnight fast and after an oral glucose load. In the normal subjects, myocardial ^{11}C palmitate in the early rapid phase of redistribution fell by 43% and the tracer clearance half-time increased by 46%. In 9 patients, the response was similar to that in normal controls. In 7 patients, however, there was a "paradoxic" response characterized by a 30% increase in the myocardial tracer content in the early rapid phase of clearance and a 36% decline in clearance half-time. The reason for the paradoxic response, which was independent of the cause of disease, but which was most apparent in the patients with the most depressed ventricular function, was unclear to these investigators. They suggested that the response might be related to a depression of citric acid cycle activity in severe cardiomyopathy.

Perloff and colleagues studied patients with Duchenne's muscular dystrophy with PET, employing ^{18}F deoxyglucose and ^{13}N ammonia.[173] They found that ^{13}N ammonia activity was selectively decreased in the posterobasal and posterolateral walls of the left ventricle in 13 of 15 patients, and that ^{18}F deoxyglucose activity was increased in the same regions in 11 of 12 patients. They concluded that the patients in whom the abnormalities were demonstrated had either a reduction in regional blood flow or regional metabolic alterations in uptake and trapping, or both. These findings are of considerable interest, in view of autopsy findings in patients with Duchenne's dystrophy, which consistently demonstrate a predilection for myopathic involvement of the posterobasal and lateral left ventricular walls, with relative sparing of the ventricular septum, right ventricle, and atrial myocardium.

Studies of PET-Labeled Drugs

Recently, labeling of drugs with positron-emitting radionuclides has become possible.[174] Calcium antagonists, beta-blockers, and positive inotropic compounds can be so labeled, and their myocardial distribution can be studied with PET. Although these studies are just beginning in humans, the possibilities for regional myocardial evaluation of drug affinity or receptor concentration are exciting.

Summary

Positron emission tomography is a complex diagnostic method that is still in its infancy. Major technical problems remain to be solved. Improved spatial and temporal resolution will be required before PET can be applied effectively to the evaluation of a number of disorders of particular concern to pediatric cardiologists, such as subendocardial ischemia in aortic stenosis or the regional myocardial metabolism of congenital heart disease in infants. However, much progress has been made with the development of PET and there is good reason to expect that this progress will continue.

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CHAPTER 52

Computed Tomography

Barry D Toombs

One of the most important advances in medicine of the recent past has been the development and refinement of computed tomography (CT) scanning. When first introduced in 1973, CT promised to revolutionize noninvasive diagnosis of diseases occurring inside the body. Pioneering work in back-projection mathematics by Godfrey Hounsfield made this new technique possible.[1] For the first time, roentgen rays were coupled with a computer for the purposes of both generation and processing, thereby creating a digital image. CT was the first of a new group of digital imaging devices that now includes computerized sonography, magnetic resonance imaging, positron emission tomography (PET scanning), digital radiography, and digital subtraction angiography.

In current CT scanners, a moving roentgen ray tube mounted in a circular housing called a gantry sends a thin fan-shaped roentgen ray beam through the centrally positioned patient. After passing through the patient, the roentgen ray beam impinges on an array of receptors (detectors) in the gantry on the opposite side of the roentgen ray tube (Fig. 52–1). Electronic signals produced by the detectors are then sent to the computer for processing. An image or "slice" created on a digital matrix is then displayed on a television monitor. Because the image data are stored in a computer, one can interact with the data to alter the image display and to perform a variety of anatomic and physiologic calculations.

CT provides unique three-dimensional anatomic information that is not available from other sources. CT is useful in imaging virtually all the structures in the body, especially those with little spontaneous motion. Cardiac imaging requirements are far more demanding than those for other parts of the body because of the rapid, complex movements that take place during each cardiac cycle. This is one reason why other imaging techniques with high sampling rates including cineangiography and two-dimensional echocardiography are better suited for cardiac diagnoses. Current conventional CT scanners take 0.6 to 5 s to obtain only one scan, and there is generally an interscan delay of at least 1 s before the next scan can begin. These factors have limited CT's utility in the evaluation of intracardiac disorders such as intracardiac shunts, valvular abnormalities, and some myocardial diseases. However, CT can provide useful information about many other diseases affecting the heart, great vessels, and mediastinum.

One advantage of CT over some of the other imaging techniques is its three-dimensional capability. A series of sequential images can be "stacked" on one another, creating a cubic matrix or volume. Once the volume has been created, one can manipulate data to display images in virtually any plane.

Another advantage that CT possesses is its superior contrast resolution, that is, its ability to separate tissues that are only slightly different in their roentgen ray absorption characteristics. Also, CT uses a tomographic technique that eliminates undesirable overlap from adjacent structures.

PERFORMING CT SCANNING

CT scanning is well tolerated by most patients, but the patient should answer several preliminary questions before commencement of the CT examination. A brief history and pertinent physical examination are useful in tailoring the CT examination to the patient. Questions about prior intravascular iodinated contrast tolerance should be answered, and a recent serum BUN and/or cre-

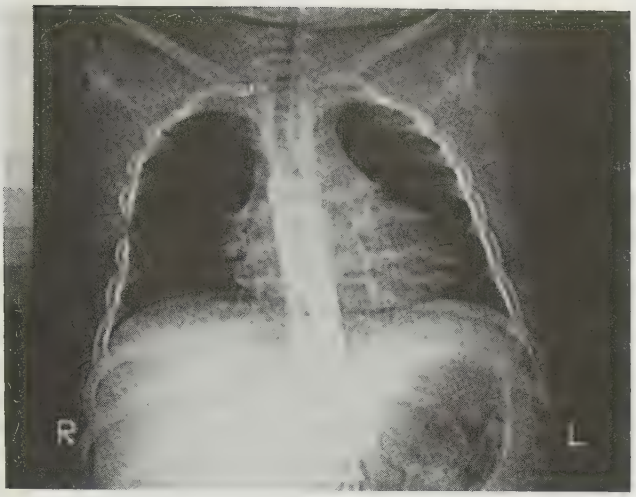


Fig. 52–1. A digital radiograph of the chest. This image is produced as the patient is moved through the scanning gantry while the roentgen ray fan beam is turned on. The image is displayed on the monitor. The vertical scale on the right of the image is a reference scale in centimeters.

atinine should be available. If the patient has had a prior contrast reaction, the nature of the reaction should be elucidated. If the reaction was mild—for example, hives, vomiting, or mild facial swelling—we generally give intravenous diphenhydramine hydrochloride (Benadryl) (1.5 mg/kg) and 25 to 100 mg of hydrocortisone sodium succinate (Solu-Cortef) before injection of contrast. For patients with histories of severe contrast reactions (hypotension, laryngospasm, and/or pulmonary edema), careful reassessment of the necessity of the examination is made; CT of the heart and mediastinal structures is very limited without the use of IV contrast. If the examination is still deemed necessary despite the increased chance of significant allergic reaction, the patient should be treated with diphenhydramine hydrochloride (Benadryl) (1.5 mg/kg, maximum 50 mg) and dexamethasone (Decadron) (0.1 mg/kg, maximum 4 mg) given orally four times a day for 48 hours prior to CT scanning.

Sedation

Patients must be as still as possible during the scanning sequence, since motion dramatically degrades the quality of the images. Generally, this means that patients under 5 years of age and others who cannot cooperate must be sedated to ensure the quality of the scan. Sedation can be obtained by using oral chloral hydrate or an intramuscular injection of meperidine hydrochloride (Demerol), promethazine hydrochloride (Phenergan), and chlorpromazine hydrochloride (Thorazine) (DPT).[2] In patients with seizure disorders, Phenergan and Thorazine are omitted, and hydroxyzine is substituted at a dose of 0.1 mg/kg. If the patient remains uncooperative after the initial chloral hydrate or DPT dose, droperidol (Inapsine) can be given parenterally, usually in 0.25-mL increments up to 0.11 mg/kg. Occasionally, other tranquilizers are required.

Opaque devices including monitor leads, snaps, and nasogastric tubes should be positioned away from the area of interest prior to scanning.

Intravenous Contrast

Intravenous contrast is an extremely important part of the CT study, since it provides a means for distinguishing flowing blood from other structures such as myocardium, vascular walls, thrombus, thymus, and mediastinal soft tissues. Without IV contrast, intravascular lesions including thrombi, neoplasms, and dissections cannot be fully evaluated, and other conditions such as pericardial and mediastinal masses cannot be seen optimally.

When possible, a relatively large-bore IV cannula is preferable because the contrast medium to be injected is rather viscous, and larger IVs allow greater flow rates. For many cardiac and mediastinal studies, a modified dynamic infusion of 0.5 to 1.0 mL/s of meglumine iothalamate is given up to a total of 2 mL/kg. When the modified dynamic scanning sequence is to be used, scanning is commenced after 50% of the total amount to be infused has been injected. Scanning then proceeds in a dynamic fashion with the shortest scan times and interscan delays possible until the total area of interest is scanned.

For certain conditions such as suspected aortic dissection, intracardiac tumors, and in some cases a congenital heart disease, a bolus injection of a higher-density contrast (at least 75%) is used. One third of the total amount of contrast to be given is injected rapidly at rates up to 4 to 5 mL/s, and serial scans are obtained at one level of interest. This method is called dynamic CT scanning.[3]

Digital Radiography

After the patient is placed on the table in the CT scanner and prior to IV contrast administration, a preliminary image is taken using the roentgen ray beam and detectors while the table is moved through the gantry. The resultant digital radiograph displayed on the CT monitor looks similar to a conventional roentgenogram. This digital image is annotated in 1-cm markings (Fig. 52–1). Digital images of the chest can be obtained in either the anteroposterior or lateral projection and serve as references for locations to be scanned. The anatomic limits for scanning are chosen from the digital radiograph, and scanning begins after the venous contrast infusion is initiated. The computer registers each image slice with a longitudinal scale on the digital radiograph. Scan slices that are 5- or 10-mm thick are obtained consecutively at contiguous levels.

GATED CT

Conventional CT scan times are long in relation to the beating of the heart. Attempts have been made by several groups to overcome this deficiency by gating the cardiac image.[4–8] Each of the methods is similar in that data are collected from the same phase of several cardiac cycles during several continuous revolutions of the CT scanner. Typically, the CT scanning system is modified so that the roentgen ray tube rotates continuously for three to five revolutions, during which time data are collected. Data collected during a certain phase or "window" of the cardiac cycle are added together to form an image. Late diastole is usually chosen as the window because it is a relatively large segment of the cardiac cycle during which relatively little motion is occurring. The angular projections obtained during the chosen phase of the cardiac

cycle are summed together along with corrective algorithms for missing projections, producing an image.

Some reports have suggested that gated CT offers advantages over conventional CT.[6-8] Oyama and colleagues[7] have found that gated CT was superior to conventional CT in a variety of cardiovascular disorders in 39% of positive cases and in 33% of negative cases. However, the time for each scanning level is rather lengthy, since the roentgen ray tube is heated often to its limit and therefore must be given several minutes to cool prior to additional scanning.

Other problems include increased exposure of the patient to radiation over that required for conventional scanning by a factor of at least three. Also, reconstruction time for each image is rather long and cumbersome. The images obtained appear to be only slightly better than standard CT. However, in some cases, only slight improvement of the image quality may be enough to make a scan diagnostically useful, particularly in cases of intracardiac masses and in some cases of myocardial infarction.

Interest in gated CT has waned considerably since the advent of Cine-CT scanning and magnetic resonance imaging (MRI).

FAST CT SCANNING

Interest in the development of a rapid CT scanning device began soon after the development of the CT scanner and reached a milestone in the development of the dynamic spatial reconstructor (DSR) at the Mayo Clinic in the mid- to late 1970s.[9,10] This research device uses an array of roentgen ray tubes in a gantry that rotates at 15 revolutions per second around the object scanned. The roentgen ray tubes are operated in rapid succession to obtain fast scanning. The roentgen ray signal detected is recorded by 14 imaging chains such that a three-dimensional composite image of the heart is produced every 60 ms. The DSR can obtain images at even shorter intervals, as little as 16 ms. Images are created in a 128 matrix format taken from the 128 × 128 × 128 cubic volume of the area scanned. Work with the DSR has proven that it is extremely accurate in the evaluation of left ventricular mass, chamber volumes, and congenital and acquired heart disease, and in coronary artery size and flow assessment.[9-13]

Recently, a new design in rapid CT was developed by Douglas Boyd, which became commercially available as Cine-CT.[14] The details of this device are given in Chapter 38. Briefly, an electron gun produces an electron beam that is magnetically deflected and swept across one of four semicircular tungsten plates (Fig. 52–2). Two 8-mm roentgen ray fan beams are produced that are transmitted through the patient and collected by two arrays of solid-state detectors positioned in the gantry above the patient. Two continuous 8-mm-thick scans can be obtained in 50 ms, and additional scans can be performed after only an 8 ms interscan delay.

Cine-CT can operate in one of several modes because the scans can be synchronized with the EKG.

In the *flow mode,* one to four levels of the heart are chosen for scanning, and two scans are obtained at each of these levels each time the EKG reaches a certain phase (usually end-diastole). In this way, when scans are obtained at the same cardiac phase over 8 to 20 heart beats, sequential flow of the injected IV contrast is demonstrated through the cardiac chambers. This mode is useful for displaying anatomic and physiologic diseases in which data analysis programs are employed. Region-of-interest cursors placed over the anatomic site to be studied in the sequential flow mode provide time–density curves with precise gamma-variate fit for quantitative and qualitative information on blood flow. Cardiac output,[15-17] patency of arterial grafts,[18-22] myocardial perfusion,[17,19,20] intracardiac shunts, and shunt calculations[21,23-26] can be measured.

Cardiac output is calculated by using the time–density curve evaluation given by the Stewart-Hamilton equation $CO = KQ/A$, where CO = cardiac output; K = calibration factor; Q = amount of contrast injected; and A = area under the curve.[15-17] These calculations are performed automatically by the software in the computer as a region-of-interest cursor is placed over either the left ventricle or the aorta. In an experimental study, this method was highly correlated ($r = 0.92$) with simultaneous thermodilution measurements.[15]

Quantitation of intracardiac shunts can also be performed by time–density curves with gamma-variate fitting. In a laboratory using surgically created right-to-left shunts in canines, there was

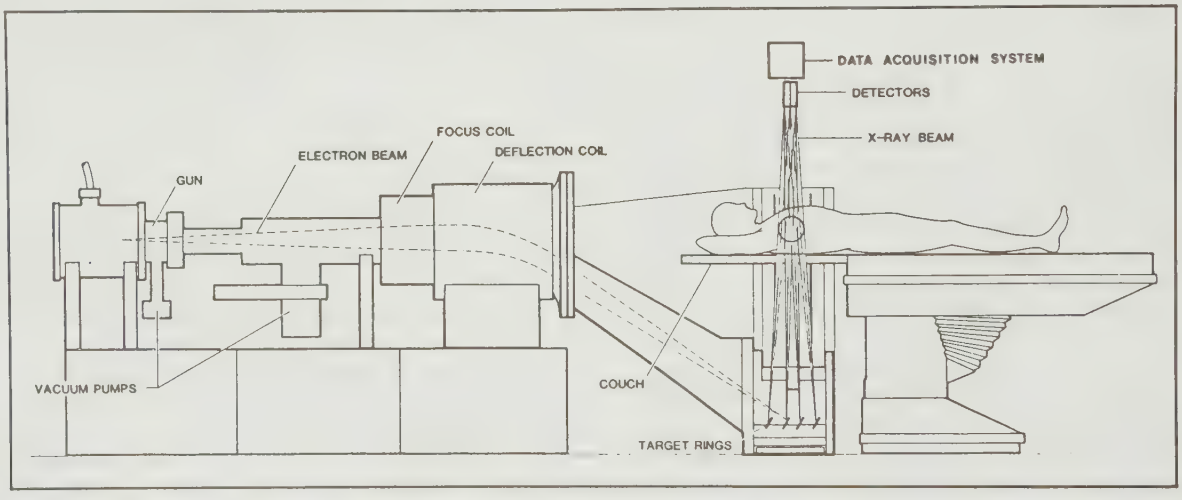


Fig. 52–2. Diagram of the Imatron Cine-CT scanner. An electron gun produces an electron beam that is focused and then deflected onto the target rings beneath the patient. Roentgen rays are produced as the electron beam is swept across the rings and, after passing through the patient, is collected by the detectors. (Courtesy of the Imatron Inc., South San Francisco, CA.)

excellent agreement ($r = 0.91$) with oximetric values over a wide range (0 to 50%).[26]

In the continuous or *cine mode,* multiple scans are obtained at two, four, six, or eight levels at a rate of up to 17 per second. Following reconstruction, the scans can be played back sequentially in a movie loop displaying dynamic cardiac function. Left and right ventricular function,[17–19] cardiac output, valvular regurgitation measurements, volume determinations, and some valvular motion abnormalities can be displayed by this mode. In contrast to the flow mode, in which cardiac output is determined by the Stewart-Hamilton equation, cardiac output in the cine mode is calculated by the heart rate times stroke volume. The entire volume of the ventricle is scanned, and cavity measurements are made at each level at both end-systole and end-diastole. Stroke volume is then calculated on the basis of Simpson's rule.[17,19] Cardiac output determinations using both the flow and cine modes are limited, however, in the presence of valvular regurgitation and intracardiac shunting.

Ejection fractions are also determined in the cine-mode by tracing the volumes calculated from scans performed through the left ventricle or right ventricle using the conventional formula

$$\frac{\text{end-diastolic volume minus end systolic volume}}{\text{end-diastolic volume}}$$

The calculated ejection fraction using Cine-CT is highly correlated with biplane angiography and exceeds equilibrium radionuclide ventriculography by a factor of approximately 8% because of the left atrial overlap on radionuclide studies.[27]

In the *volume mode,* the table is moved rapidly through the gantry while one target ring is rapidly scanned. This permits the acquisition of up to 80 slices covering 64 centimeters of anatomy. From these data, images can be reformatted in any operator-selected plane. Relationships of the cardiac chambers and great vessels, masses, and abnormal fluid collections can be determined as well as patency of surgical shunts.[3,17,21]

CLINICAL CASES

Conventional CT scanning is often used to provide additional anatomic information about diseases of the chest. Intrinsic subject contrast of the various mediastinal structures is quite low because attentuation values of the heart and normal mediastinal structures are similar and contrasting mediastinal fat is usually sparse in children. To compensate for this low-contrast state, IV contrast is used to opacify the great vessels and cardiac chambers. This allows separation of the great vessels from pathologic and normal mediastinal structures. When IV contrast cannot be given in large quantities, there are significant limitations in detecting and defining pathological processes in the mediastinum (Figs. 52–3 and 52–4).

In conventional CT, motion artifacts from physiologic motion and from moving radiopaque catheters degrade the image, decreasing the definition of the heart and, to a lesser extent, the great vessels (Fig. 52–5). Conventional CT is best applied to a number of mediastinal and pulmonary masses such as pericardial lesions, tumors of the mediastinum and heart, and great vessel abnormalities.

Pericardial Lesions

Echocardiography has proven extremely useful in the diagnosis of pericardial disease, especially in pericardial effusions. However, CT is even more sensitive to a wide variety of diseases affecting the pericardium, including pericardial thickening, calcification, and other pericardial masses.[28–33] In one study of eight patients, CT demonstrated pericardial masses in all patients, whereas echocardiography was abnormal in only one of the seven patients studied. In restrictive pericardial disease, calcifications of the pericardium may be seen with CT that cannot be observed with echocardiography (Fig. 52–6).

Pericardial effusions are often better seen with CT. Adipose tissue may produce anterior and/or posterior echo-free spaces on echocardiography, resulting in a false-positive reading for pericardial effusion. These areas, however, are properly displayed as fat containing on CT.[32] Effusions from a variety of conditions including trauma (Fig. 52–7),[34] thickening from infection (Fig. 52–8),[35] and solid and cystic neoplasms (Fig. 52–9) are easily seen. Partial or complete absence of the pericardium can also be suggested on CT.[36,37]

Great Vessels

Assessment of the position and patency of the great vessels is usually easily displayed with CT. While echocardiography provides examination of the proximal great vessels, changes affecting the more distal portions of the great vessels can often be better displayed on conventional CT and Cine-CT. Acquired conditions such as superior vena cava thrombosis (Fig. 52–10), congenital variations such as right aortic arch (Fig. 52–11), aberrant subclavian vessels (Fig. 52–12), persistent left superior vena cava (Fig. 52–13), and some anomalous veins can be often visualized with conventional CT[3,23,37–42] and Cine-CT.[21–23] Also, coarctations can be seen on conventional dynamic CT scanning[43] (Fig. 52–14) and with Cine-CT (Fig. 52–15) performed in the volume mode. In coarctations, reformatted off-axis images formed in the plane of the thoracic aorta are useful to demonstrate the proximally dilated brachicephalic vessels, the coarctation, and the diminutive descending aorta. Sagittal MRI may prove even better than CT for detecting coarctations.

The diagnosis of aortic aneurysms and aortic dissections is more precisely made with dynamic CT scanning than with any other technique.[43–45] For suspected thoracic aortic dissections, a dynamic scanning sequence performed with a conventional CT scanner at three different levels in the aorta following contrast injection can provide exquisite detail (Fig. 52–16). The information derived from the dynamic scanning sequence provides morphologic as well as physiologic information.[3,44–46] CT offers advantages over conventional aortography in dissections in that it is noninvasive, takes only 10 to 15 minutes to complete, and demonstrates hematomas and thrombosed false lumen that may be quite difficult to see by angiography. In one study done on an older CT instrument, CT was more sensitive in detecting dissections than aortography (83% versus 75%).[44]

Some centers have advocated the use of CT in the evaluation of suspected aortic injuries in blunt trauma.[47] CT has certainly markedly improved noninvasive accuracy in the assessment of neurological and abdominal/pelvic system injuries. While the diagnosis of aortic injuries by CT remains controversial, CT can certainly document the presence of periaortic hematomas that should suggest aortic injuries (Fig. 52–17). In our experience, demonstration of the aortic pseudoaneurysm has been difficult; our

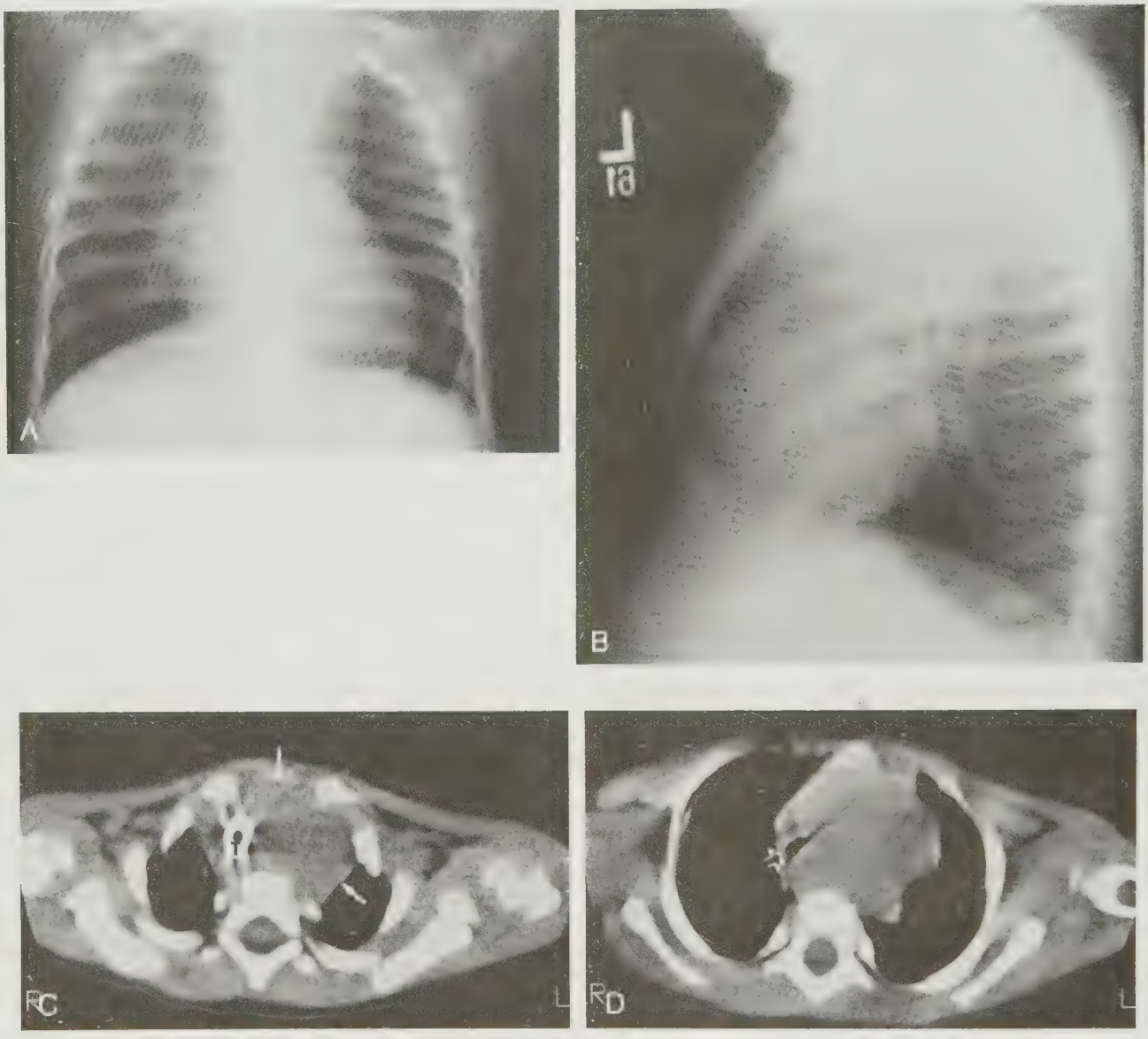


Fig. 52–3. Large neck and mediastinal hemangioma. It is poorly separated from adjacent structures because of lack of intravenous contrast. (A and B) Chest films disclose a large mediastinal mass primarily in the left paratracheal area extending down to the aortopulmonary window level. (C) A CT scan through the upper chest discloses a homogeneous left paratracheal soft tissue mass (arrows). The mass has the same density as the thoracic musculature and thoracic great vessels. The vasculature can be separated from masses when dynamic or modified dynamic scanning is used with high doses of intravenous contrast. Also notice the tracheostomy tube (T) in the trachea. R = right; L = left. (D) A CT scan 2 cm below that shown in part C discloses displacement of the trachea (arrow) to the right of midline by the homogeneous mass.

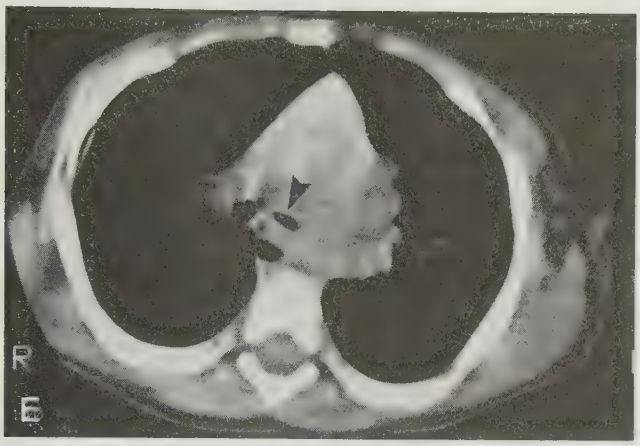


Fig. 52–3. continued. (E) A CT scan 2 cm below that shown in part (D) demonstrates a narrowed left main bronchus (arrowhead) by the hemangioma mass. (F, G, and H) Subtraction films from arch aortography in early arterial, midarterial, and capillary phases disclose the vascular mass (arrowheads) extending from the upper portion of the neck to a point below the aortic arch, compressing the left main bronchus.

Fig. 52–3. continued.

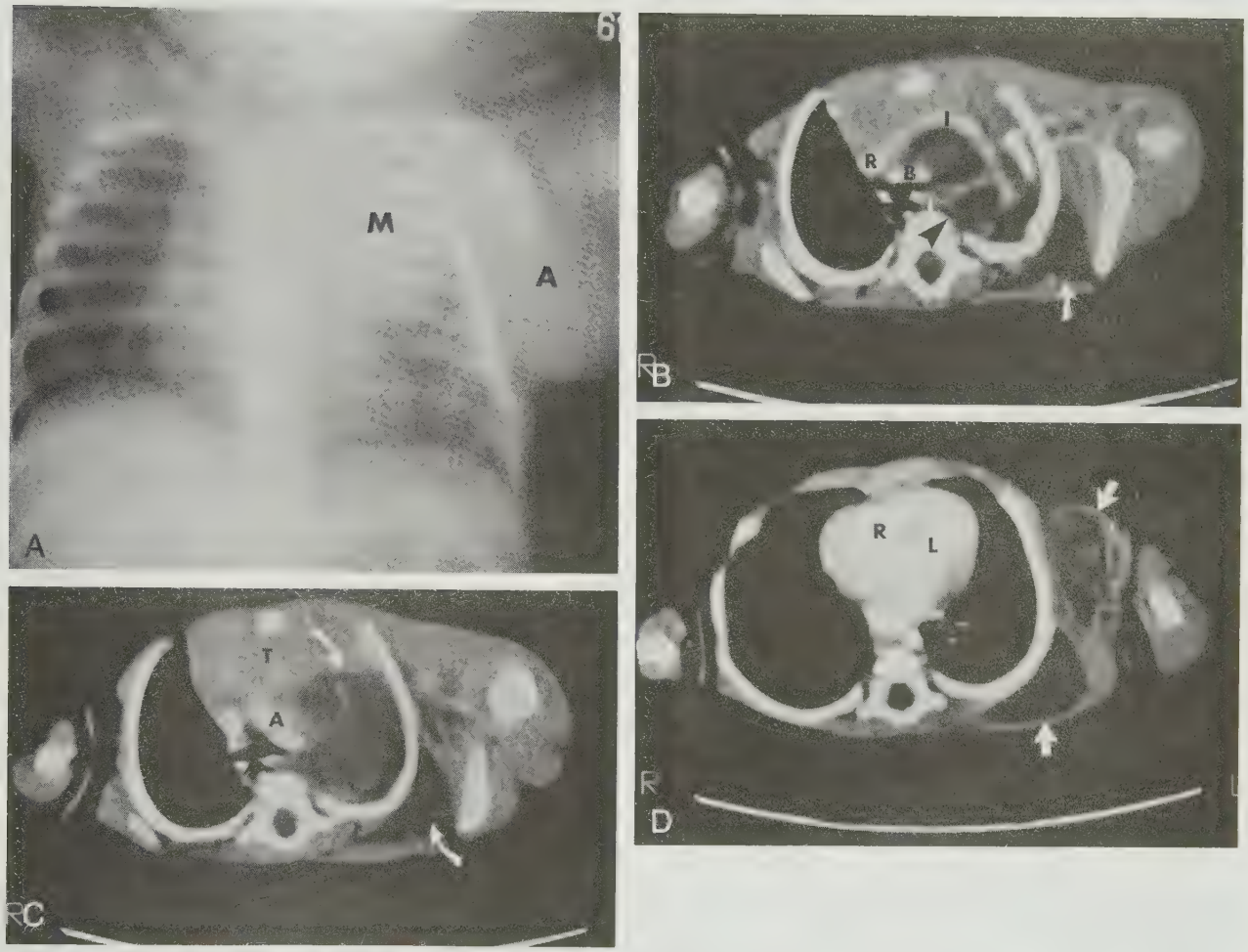


Fig. 52–4. A cystic hygroma extending into lateral axilla and mediastinum. There is excellent separation of the mass from contrast-filled great vessels. (A) Chest film discloses a left paratracheal mass (M) and a lateral axillary mass (A). (B) A CT scan of the upper chest demonstrates contrast-filled left innominate vein (I) with thymus anterior and cystic hygroma posterior extending into the left posterior axillary recess (arrows). The right innominate vein (R) and brachycephaliac artery (B) are also seen. (C) A CT scan 1 cm below that shown in part (B) using the modified dynamic technique in a 4-year-old, discloses the thymus (T), contrast-filled aortic arch (A), and low-density left superior and axillary low-density cystic hygroma (arrows) in the mediastinum and axilla. (D) A CT scan through the ventricular level shows a left axillary cystic hygroma (arrows) with mediastinal involvement at this level. Contrast right (R) and left (L) ventricles are separated by the interventricular system.

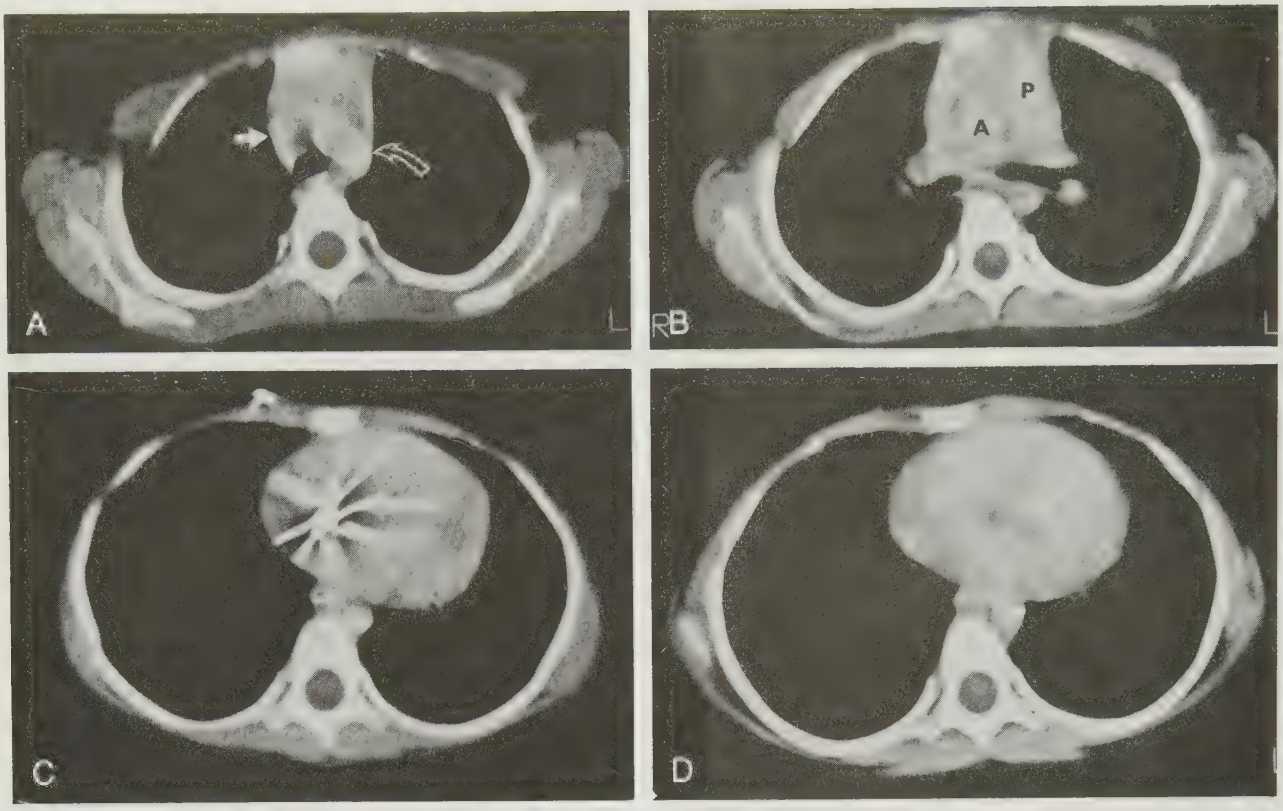


Fig. 52–5. A normal CT scan of the chest, using a modified dynamic technique. (A) A CT of the upper chest discloses aortic arch (curved arrow) and superior vena cava (straight arrow). The thymus is just anterior to the aortic arch. (B) A CT scan through the midchest just below the carina demonstrates motion and some contrast in the proximal ascending aorta (A) and main pulmonary artery (P). (C) A CT scan through the heart demonstrates a "star" artifact from a high-density moving central venous catheter in right atrium. Intracardiac morphology is poorly seen. (D) A CT scan through the heart 1 cm below that shown in part C discloses artifacts and partial visualization of the interventricular septum (arrow).

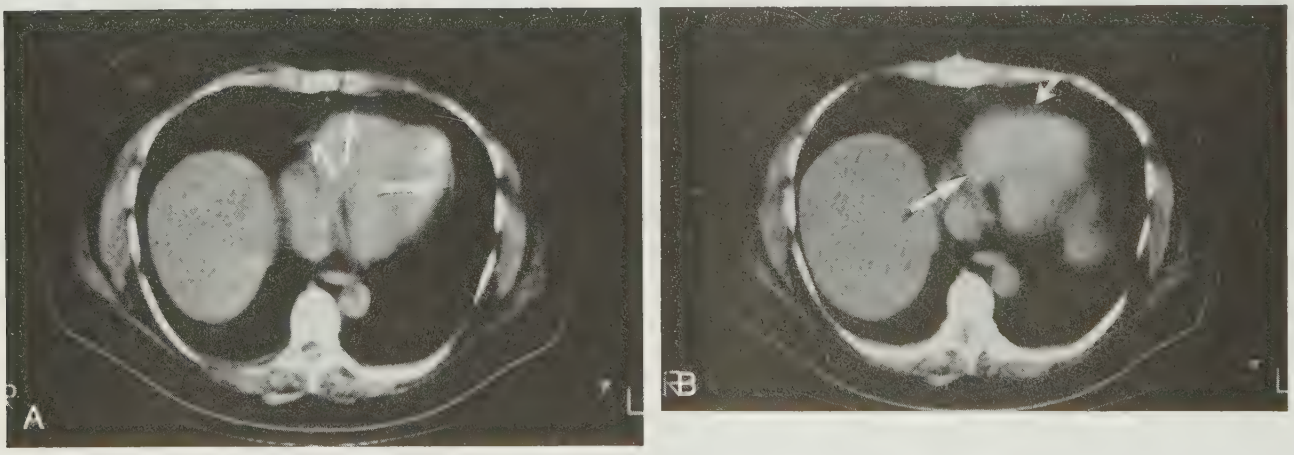


Fig. 52–6. Calcific constrictive pericarditis in a 40-year-old woman with normal echocardiography. (A) A CT scan through the level of ventricles discloses slight thickening at the pericardium medial and laterally with normal thickness anteriorly. (B) A CT scan 1 cm below that shown in part A demonstrates calcification (arrows) in the pericardium adjacent to the right atrium and ventricle.

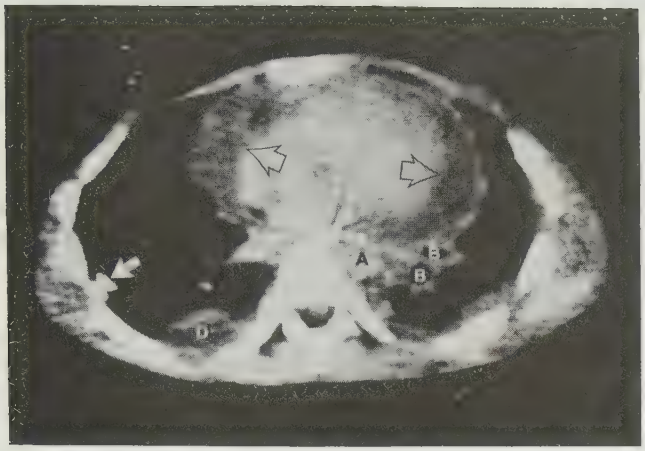
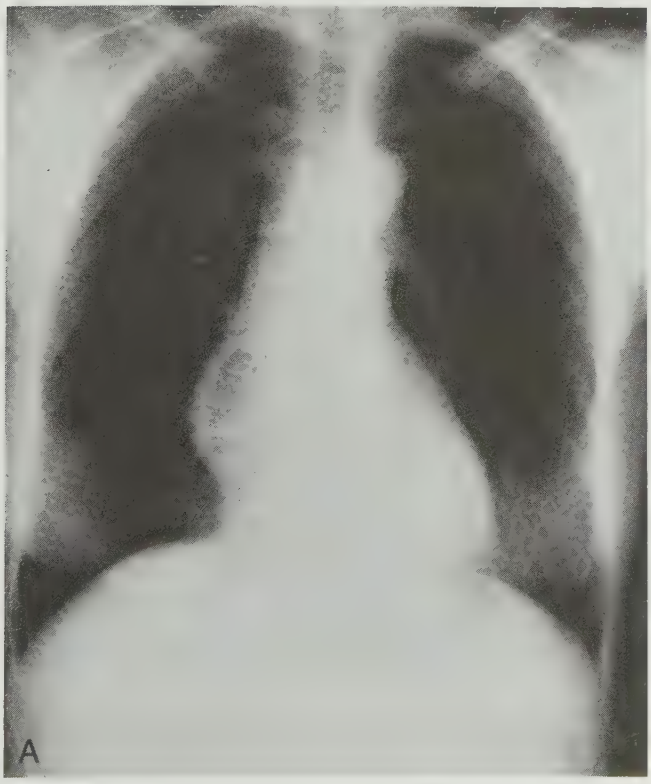


Fig. 52–7. Traumatic pericardial effusion in a 5-year-old 10 days after an auto-pedestrian accident. A low-density pericardial effusion (dark arrows) surrounds the heart. Bronchi (B), descending aorta (A), posttraumatic peripheral pulmonary density (B), and chest tube (white arrow) are also seen. (Reprinted with permission from Toombs, B.D., Sandler, C.M., and Lester, R.G.: Computed tomography of acute chest trauma. Radiol. Clin. N. Am., *140*:733–738, 1981.)

Fig. 52–8. Pericardial abscess. This patient received a gunshot wound three weeks prior to this study. Low-density abscess fluid (dark arrowheads) is seen in the pericardial space. The pericardium is thickened (white arrow). Left empyema is also present (E). (Reprinted with permission from Toombs, B.D.: Complications of chest trauma. *In* Computed Tomography in Trauma. Edited by B.D. Toombs and C.M. Sandler. Philadelphia, W.B. Saunders, 1987, pp. 84–111.)



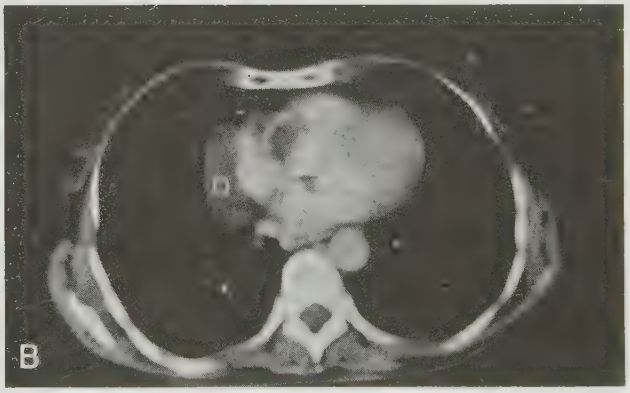


Fig. 52–9. Pericardial cyst. (A) A chest roentgenogram discloses a nonspecific bulge along the right heart border. (B) A CT scan displays low-density (0 Hounsfield units) mass (O) just lateral to the right atrium, diagnostic of a cyst.

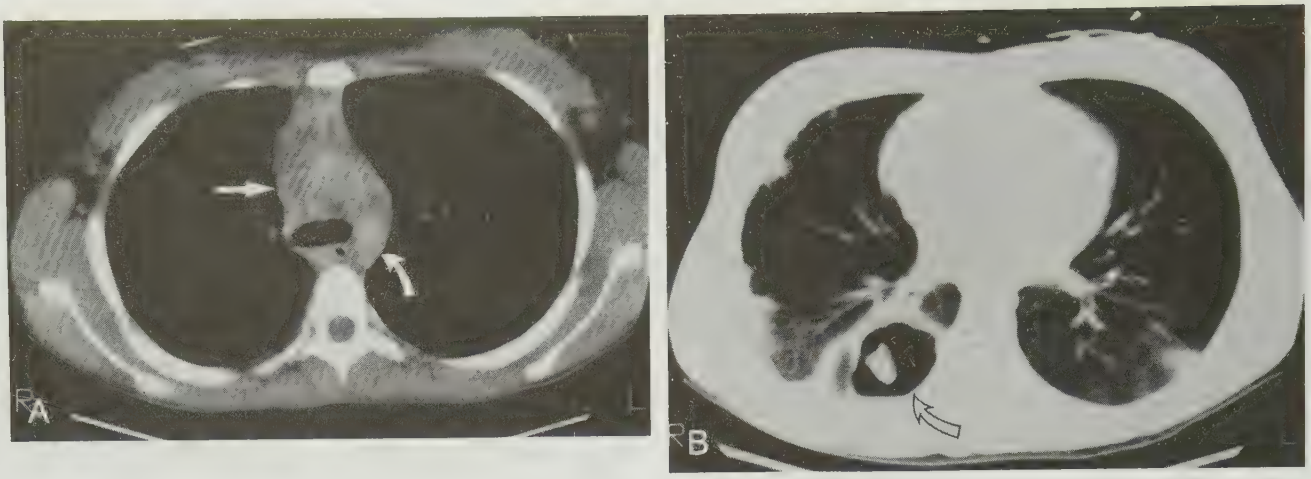


Fig. 52–10. Superior vena cava thrombosis in a 13-year-old with right lower lobe abscess. (A) A CT scan just below the level of the aortic arch demonstrates "ring-like" density (arrow) with a low-density center (thrombus) representing the superior vena cava. The descending aorta (curved arrow) is higher in density. (B) A CT scan through the level of the right lower lobe abscess (arrow), exhibiting a thick wall and internal debris.

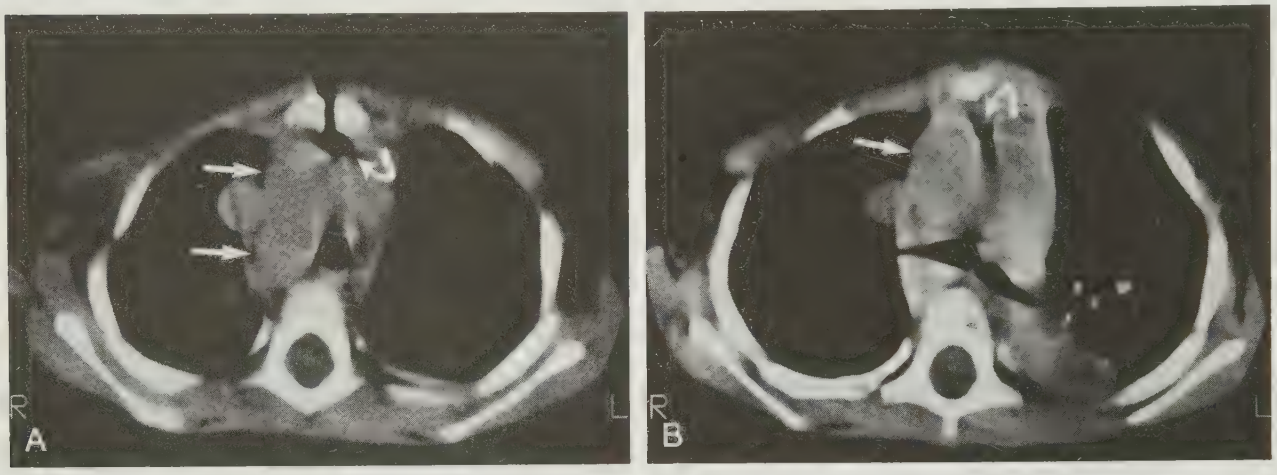


Fig. 52–11. Right aortic arch in a 2-year-old patient with tetralogy of Fallot with postoperative mediastinal abscess. No intravenous contrast was used. (A and B) CT discloses a right aortic arch (arrows) and abnormal gas in the mediastinum (curved arrows).

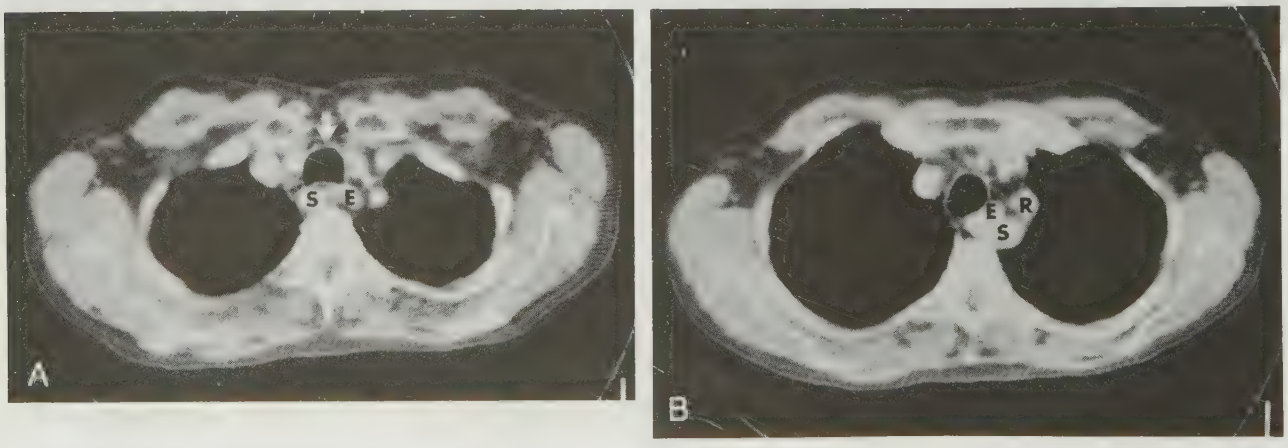


Fig. 52–12. Aberrant right subclavian artery. (A) A CT scan through the upper chest discloses the right subclavian artery (S) behind the trachea (arrow) and to the right of the esophagus (E). (B) A CT scan obtained 1 cm cardial to that shown in part (A) demonstrates the right subclavian artery (S) behind the esophagus (E) and left subclavian artery (R).

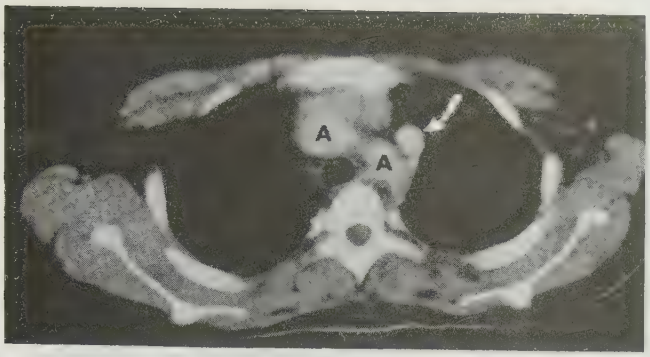


Fig. 52–13. Left superior vena cava in a 16-year-old patient. A CT image shows a left superior vena cava (arrow) adjacent to the aortic arch (A).

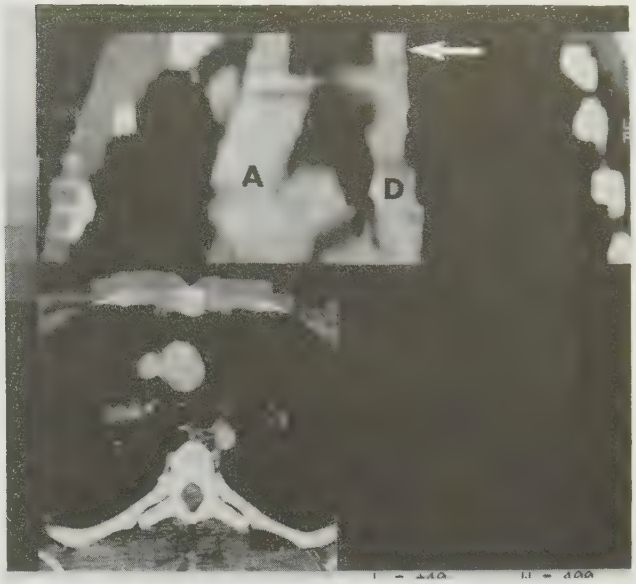


Fig. 52–14. Coarctation of the aorta, a postoperative study. CT images were obtained at 1-cm intervals, and an oblique sagittal reformatted image (upper part of image) was created through the plane outlined in the lower standard axial image. Ascending aorta (A), descending aorta (D), and persistently dilated left subclavian artery (arrow) are seen.

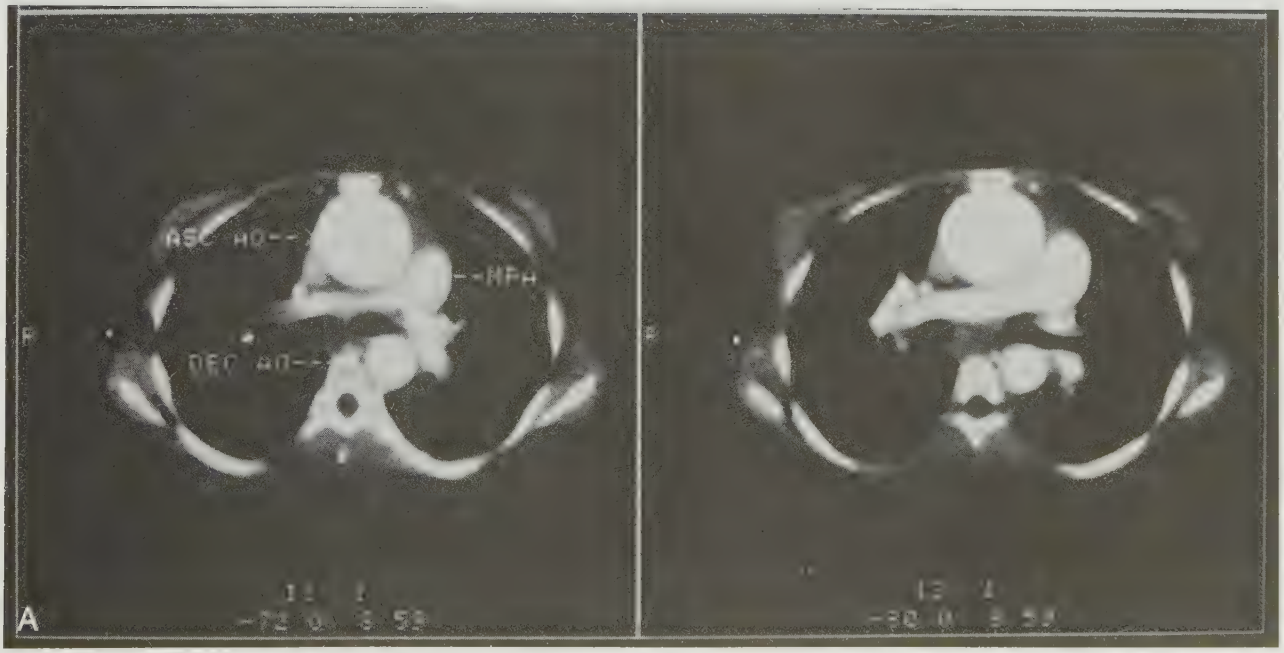


Fig. 52–15. Coarctation of the aorta, a Cine-CT study. (A) Two Cine-CT images performed in the volume mode 8 mm apart demonstrate relative dilatation of the ascending aorta (ASC AO) compared to the descending aorta (DEC AO). Also note the main pulmonary artery (MPA) that divides into left and right branches.

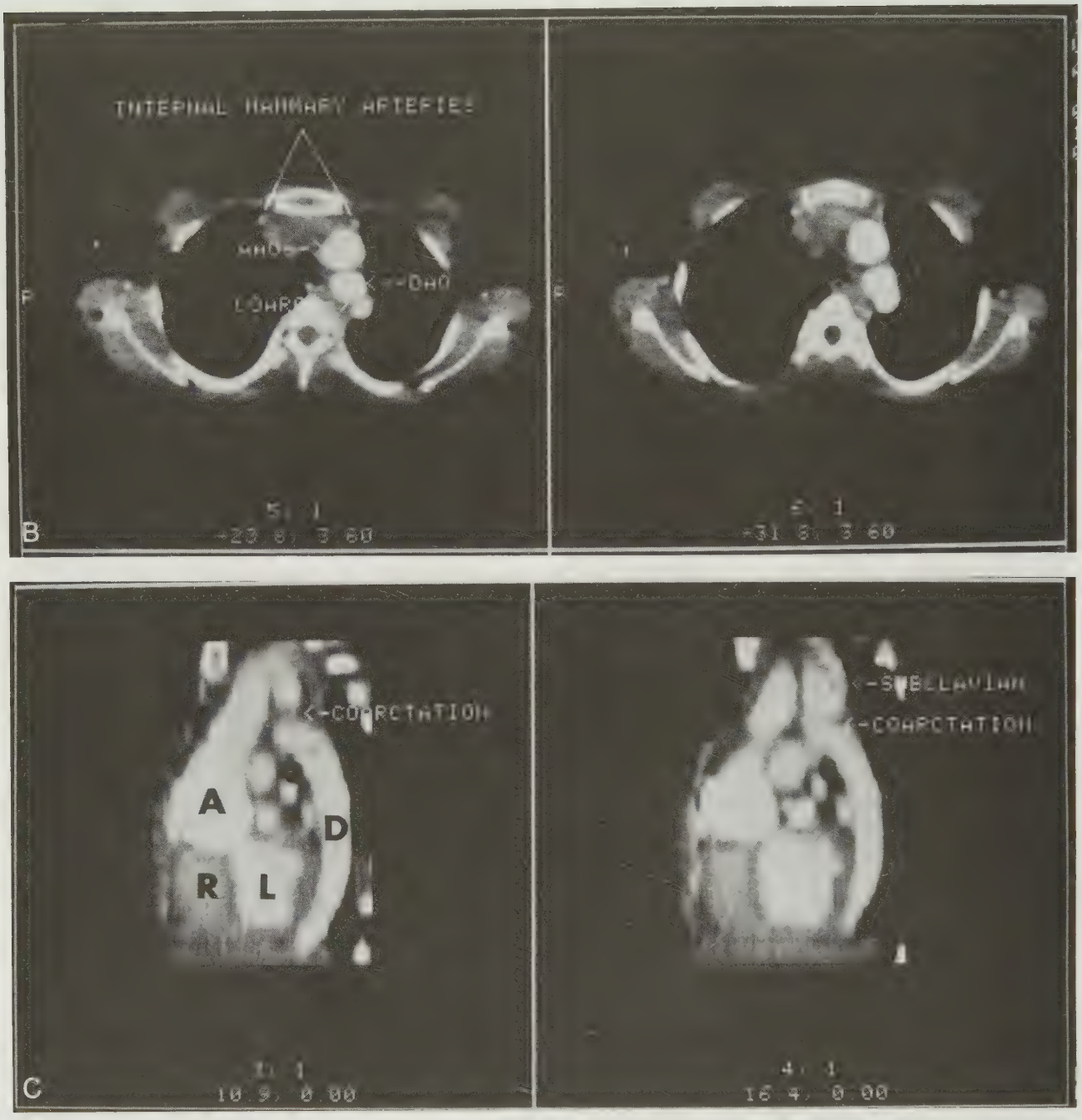


Fig. 52–15. continued. (B) A pair of Cine-CT images at the level of coarctation discloses the coarctation defect (COARCT) in the descending aorta (DAO) behind the ascending aorta (AAO). The internal mammary arteries are prominent. (C) Off-axis parasagittal reformatted images from data acquired from volume mode. Note the slightly dilated contrast-filled aortic root (A), coarctation, descending aorta (D), and left atrium and ventricle complex (L). The right atrium (R) is relatively low in density because the injected bolus of contrast has already dissipated. (Courtesy of W.J. Eldredge and S. Flicker, Deborah Heart and Lung Center, Browns Mills, N.J.)

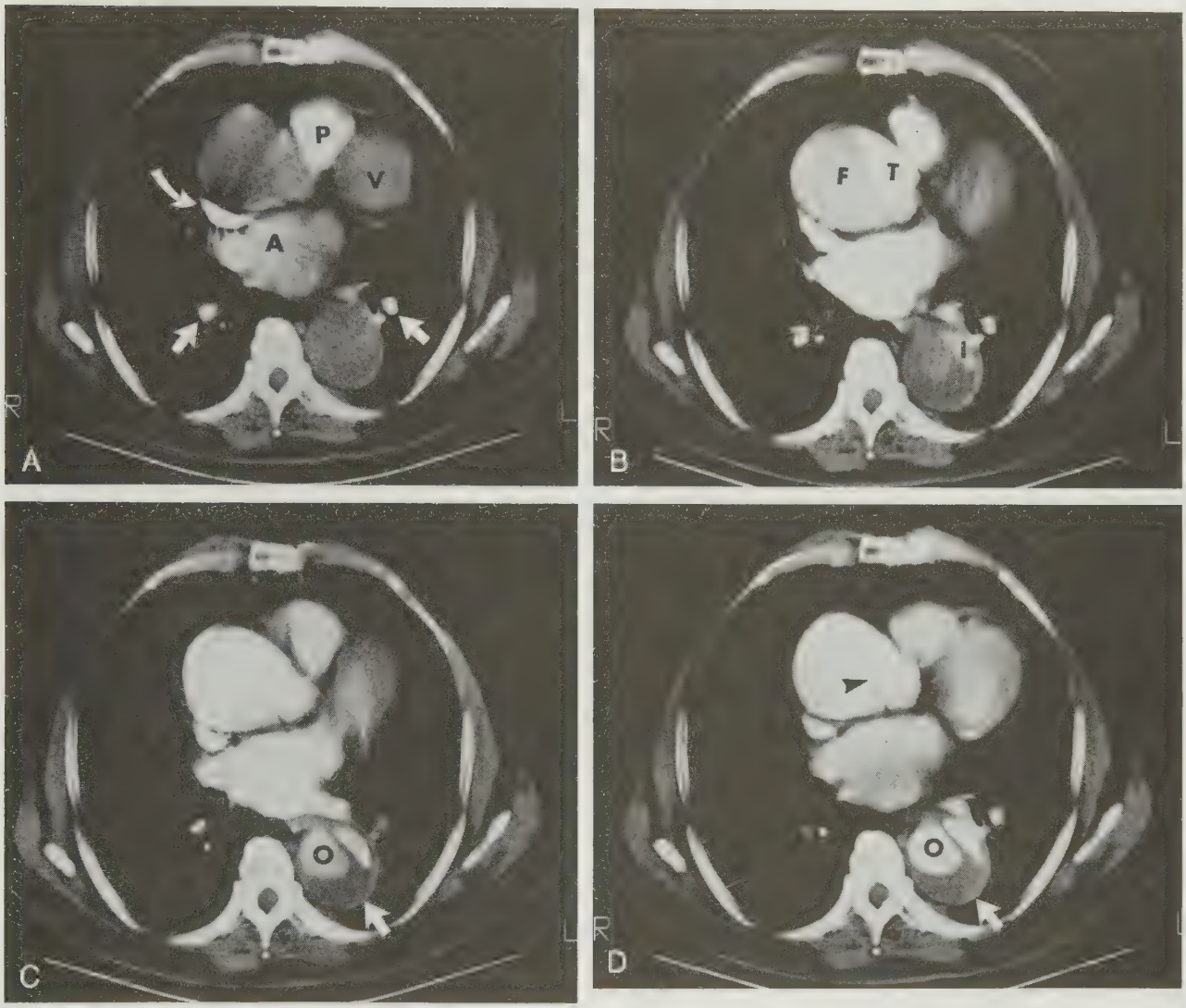


Fig. 52–16. Type A aortic dissection. Dynamic scanning at one level (proximal ascending aorta) with conventional CT scanning. (A) Early CT image 5 seconds after injection of contrast discloses contrast in the pulmonary artery (P), both lower lobe pulmonary artery branches (arrows), the superior vena cava (curved arrow), and the left atrium (A). The superior aspect of the left ventricle is also noted (V). (B) A CT scan 2 seconds after that shown in part A discloses contrast in the dilated ascending aorta in both the true (T) and false (F) lumens separated by the intimal flap. The true lumen (I) in the descending aorta is also opacified. The left atrium is better opacified than during the scan in part A. (C) A CT scan 2 seconds after that shown in part B demonstrates opacification of the patent portion of the false lumen in the descending aorta (O) and nonopacification of the thrombosed portion (arrow). (D) A CT scan 2 seconds after that shown in part C discloses the patent false lumen (O) and thrombosed portion (white arrow) with persistent good demonstration of the intimal flap of the ascending aorta (black arrowhead).

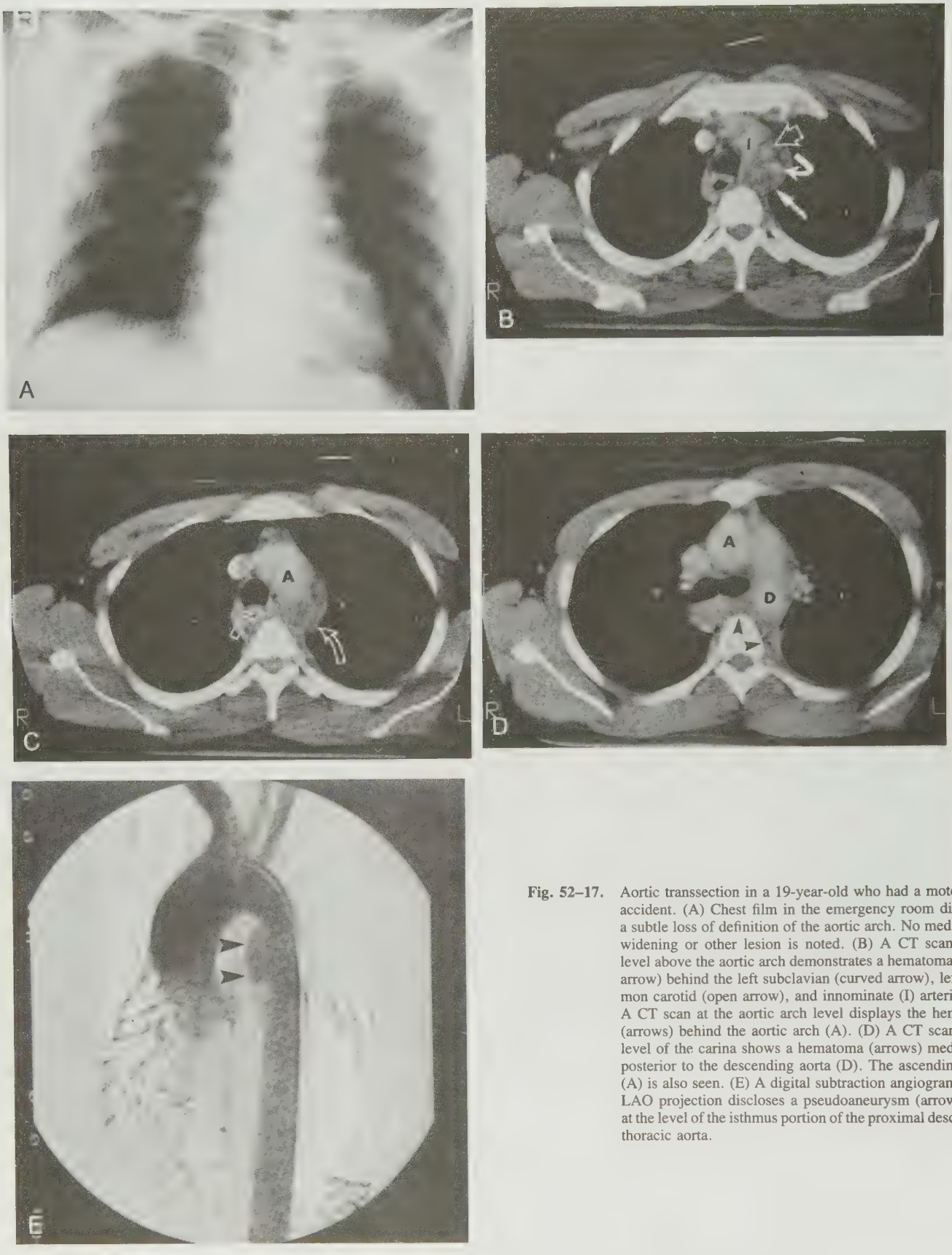


Fig. 52–17. Aortic transsection in a 19-year-old who had a motorcycle accident. (A) Chest film in the emergency room discloses a subtle loss of definition of the aortic arch. No mediastinal widening or other lesion is noted. (B) A CT scan at the level above the aortic arch demonstrates a hematoma (white arrow) behind the left subclavian (curved arrow), left common carotid (open arrow), and innominate (I) arteries. (C) A CT scan at the aortic arch level displays the hematoma (arrows) behind the aortic arch (A). (D) A CT scan at the level of the carina shows a hematoma (arrows) medial and posterior to the descending aorta (D). The ascending aorta (A) is also seen. (E) A digital subtraction angiogram in the LAO projection discloses a pseudoaneurysm (arrowheads) at the level of the isthmus portion of the proximal descending thoracic aorta.

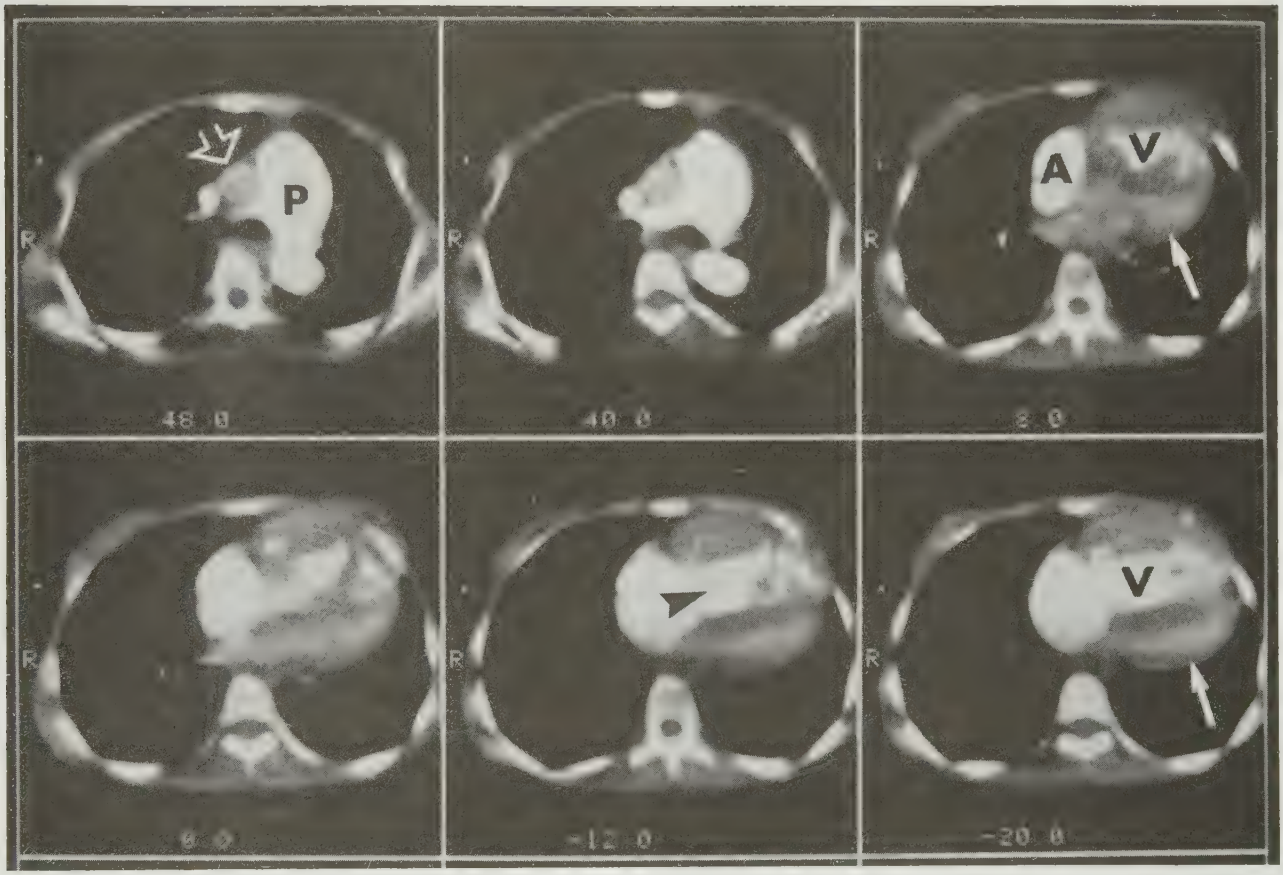
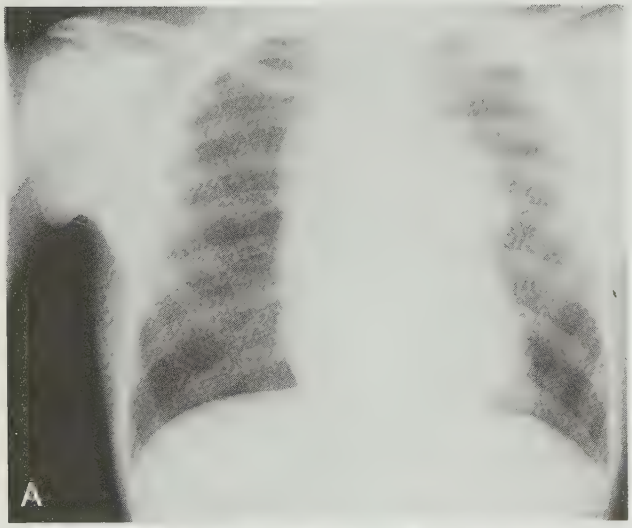
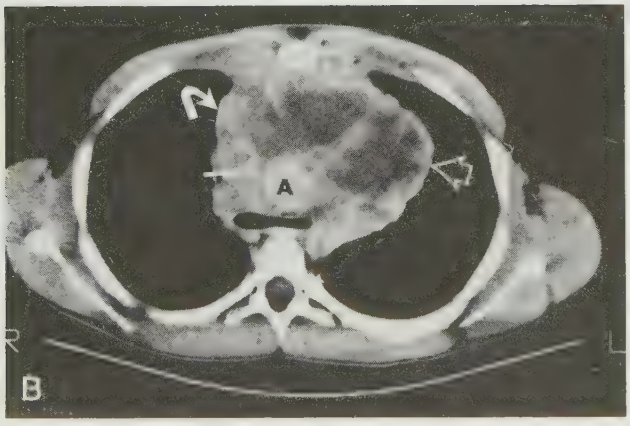


Fig. 52–18. Cine-CT of a patient with atrial septal defect and pulmonic stenosis in the volume mode. Images performed at several levels over 250 ms demonstrate dilatation of the pulmonary artery (P) compared to the ascending aorta (open arrowhead). There is hypertrophy of the contrast-filled right ventricle (V). Premature partial opacification of the left atrium (arrows) is related to the atrial septal defect. The tricuspid valve is also seen (black arrowhead). (Courtesy of Imatron, Inc. and W.J. Eldredge and S. Flicker, Deborah Heart and Lung Center, Browns Mills, N.J.)

Fig. 52–19. A Cine-CT volume study of a 7-year-old with tetralogy of Fallot. Eight scans disclose the left aortic arch (curved arrow) and hypoplastic right and left pulmonary arteries (straight arrows) arising from the borderline enlarged main pulmonary artery (:). Both the left (L) and right (R) ventricles are slightly dilated. (Courtesy of W.J. Eldredge and S. Flicker, Deborah Heart and Lung Center, Browns Mills, N.J. and of Imatron, Inc.)





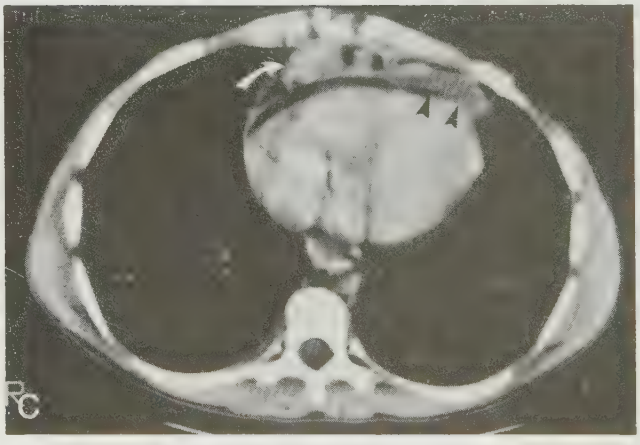


Fig. 52–20. Mediastinal masses in a 14-year-old with Hodgkin's disease. (A) Chest film exhibits asymmetric mediastinal enlargement. (B) A CT scan at the level of the carina discloses necrotic tumor masses (open arrowheads) anterior to the ascending aorta (A). The azygous vein (straight arrow) and superior vena cava (curved arrow) are distorted by enlarged lymph nodes. (C) A CT scan through the level of the ventricles demonstrates pericardial effusion (black arrowheads) just anterior to the left ventricle and adjacent low-density epicardial fat. Anterior mediastinal lymphadenopathy is also seen (curved arrow).

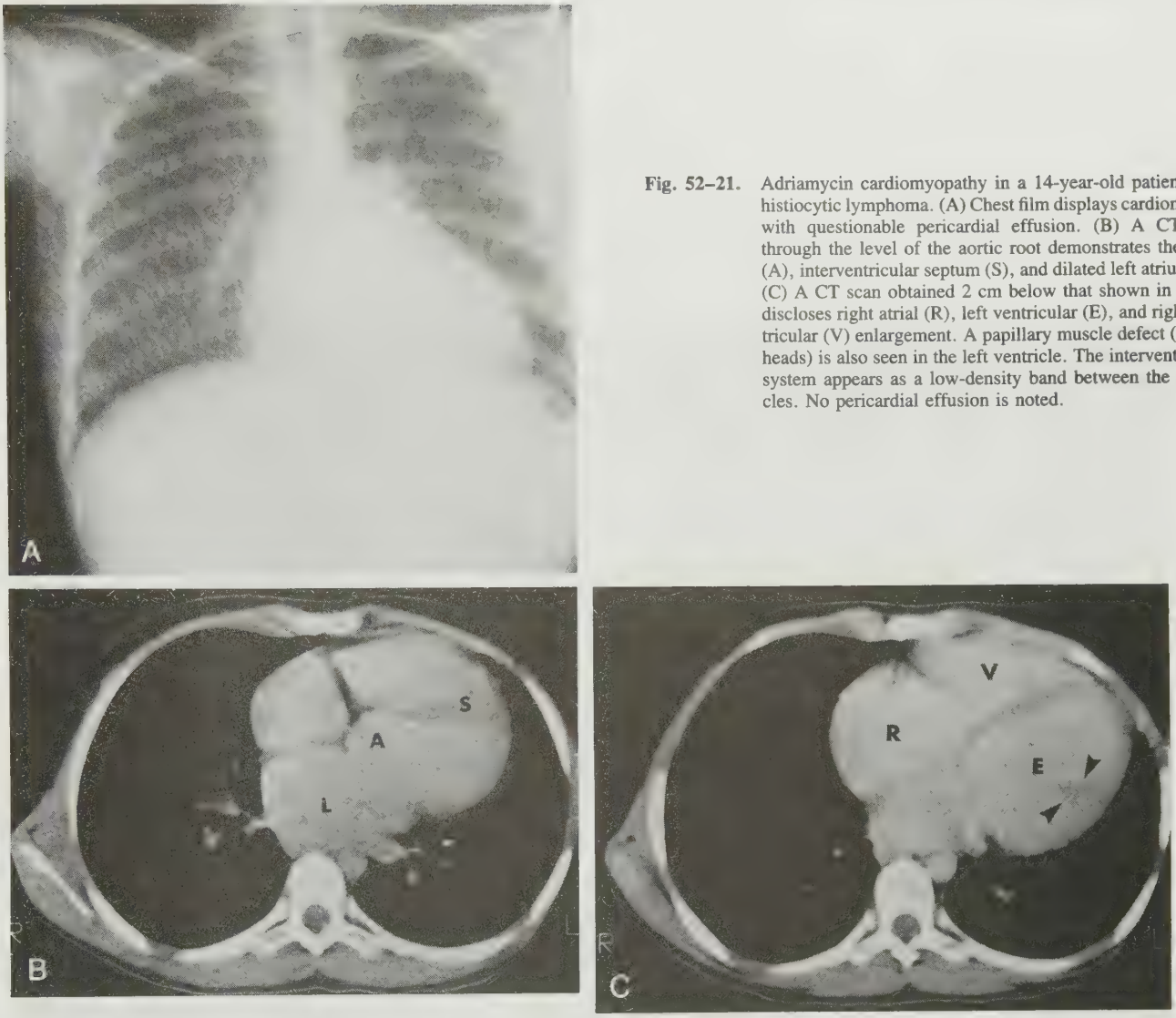


Fig. 52–21. Adriamycin cardiomyopathy in a 14-year-old patient with histiocytic lymphoma. (A) Chest film displays cardiomegaly with questionable pericardial effusion. (B) A CT scan through the level of the aortic root demonstrates the aorta (A), interventricular septum (S), and dilated left atrium (L). (C) A CT scan obtained 2 cm below that shown in part B discloses right atrial (R), left ventricular (E), and right ventricular (V) enlargement. A papillary muscle defect (arrowheads) is also seen in the left ventricle. The interventricular system appears as a low-density band between the ventricles. No pericardial effusion is noted.

current policy is that patients with suspected aortic injuries should receive urgent angiography.

Pulmonary emboli can occasionally be seen with CT when they are relatively large and affect the central vessels.[35] However, patients suspected of having pulmonary emboli should be studied with either pulmonary angiography or ventilation/perfusion scanning, since these techniques are more sensitive. In one study, however, organizing emboli in chronic thromboembolic pulmonary disease were better seen on CT than with angiography.[48]

Changes in pulmonary arteries other than emboli can also be seen both on conventional CT and Cine-CT scanning. Pulmonary valvular stenosis (Fig. 52–18), suprapulmonic stenosis (Fig. 52–19), aneurysms, and atresia have been demonstrated.[21,49]

Mediastinal Lesions

The child who presents with nonspecific clinical findings and an abnormal chest roentgenogram may require CT for additional anatomic information. Many abnormal mediastinal densities on conventional chest radiography can be properly classified into disease categories. CT is probably the most sensitive technique for detecting mediastinal lesions,[50] though MRI has shown great promise. Cardiovascular lesions can be separated from noncardiovascular lesions, including congenital cystic lesions (Fig. 52–4) and acquired tumors (Fig. 52–20). In addition, CT provides useful information about children who have neoplasms and have undergone potentially cardiotoxic chemotherapy whose cardiomediastinal silhouettes are abnormal (Fig. 52–21).

Cardiac Lesions

The development of two-dimensional echocardiography and cardiac radionuclide imaging has provided a quantum leap in the noninvasive diagnosis of pediatric and adult cardiac disease. Some conditions such as valvular heart disease and myocardial thickening or thinning that required cardiac catheterizations in the past can be estimated quite precisely with these techniques.

Dynamic conventional CT scanning has proven to be quite useful in the assessment of a variety of congenital diseases involving the great vessels.[39] However, demonstration of intracardiac congenital disorders with conventional CT including valvular processes is inconsistent. Echocardiography, cineangiography, and

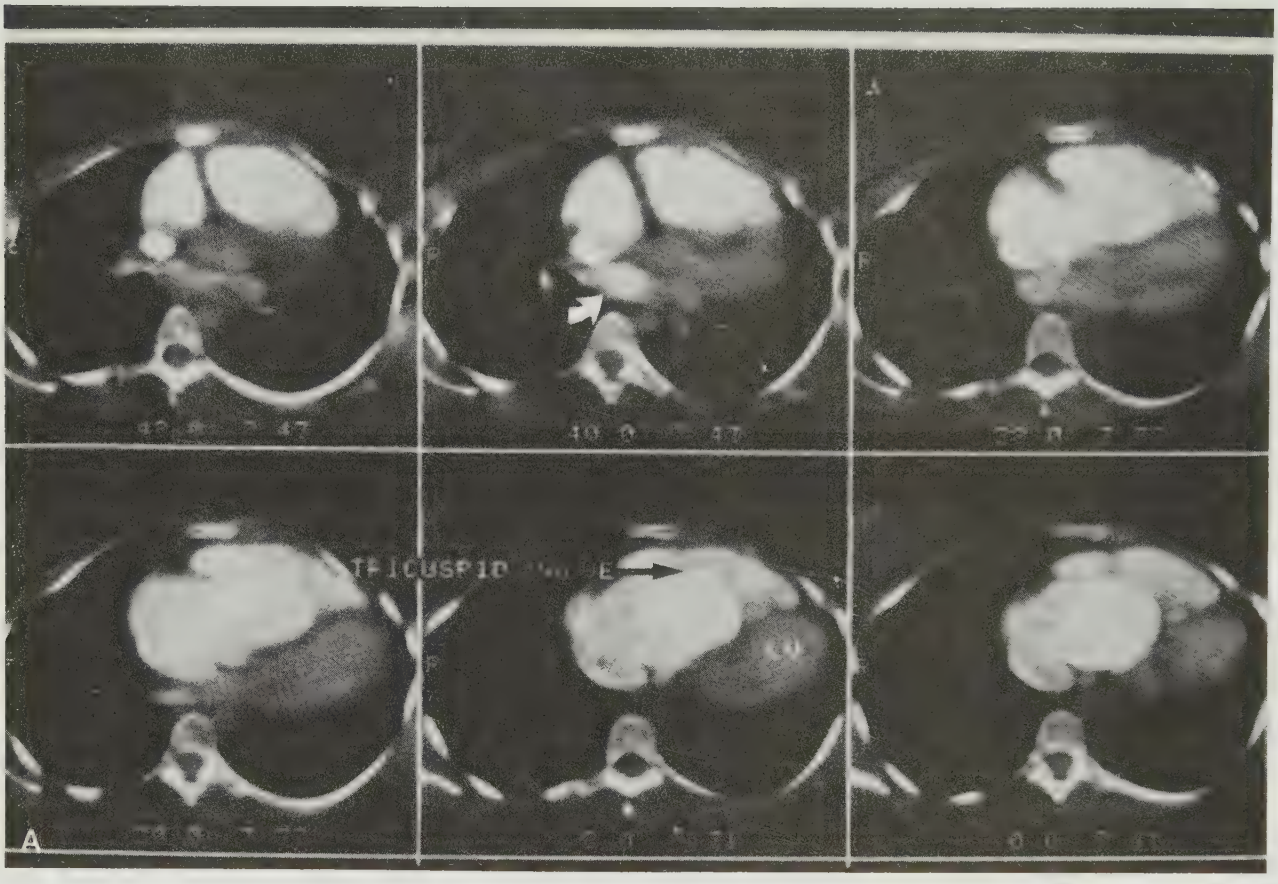


Fig. 52–22. Ebstein's anomaly with atrial septal defect in a Cine-CT study. (A) A volume mode study with six levels displayed shows enlargement of the right atrium with partial atrialization of the right ventricle (RV). The tricuspid valve is seen in an anomalous position (arrow). The left atrium (curved arrow) contains a small amount of contrast arising from the atrial septal defect.

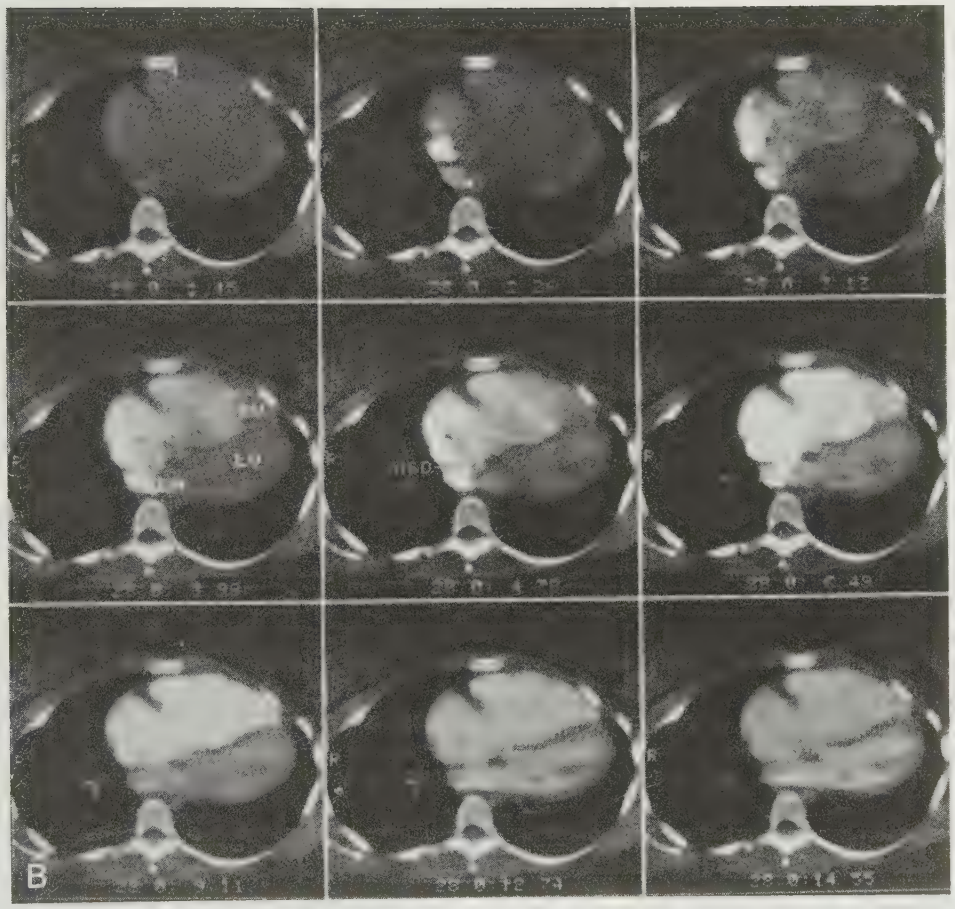
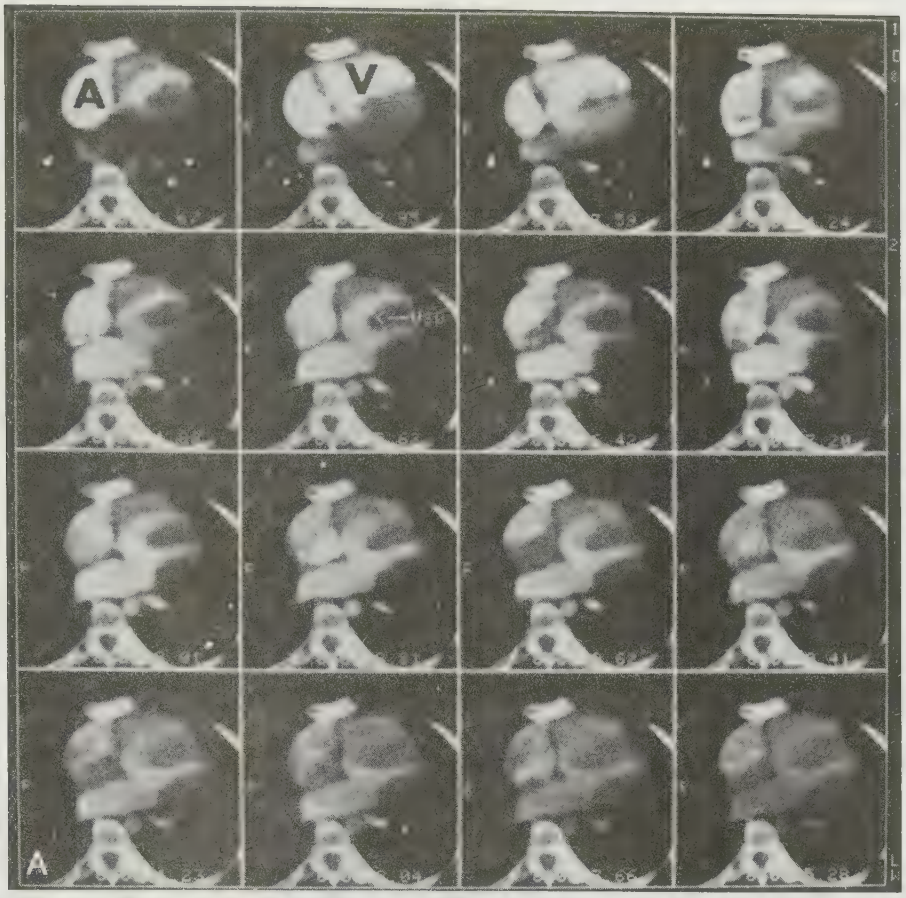


Fig. 52–22. continued. (B) A flow mode study exhibiting nine images obtained sequentially at the same level following injection of contrast. As contrast arrives, the right atrium (RA) and left atrium (LA) are opacified simultaneously. The atrial septal defect is also imaged. The right ventricle (RV) and left ventricle (LV) are also seen.

Fig. 52–22. continued. (C) Shunt calculation of atrial septal defect using time (abscissa)–density (ordinate, in CT numbers) curves. Gamma variates are placed to conform to both peaks (arrows). Computer-assisted calculations of the areas under both curves provide an estimation of shunt size. (Figures provided by Imatron, Inc. and W.J. Eldredge and S. Flicker, Deborah Heart and Lung Center, Browns Mills, N.J.)



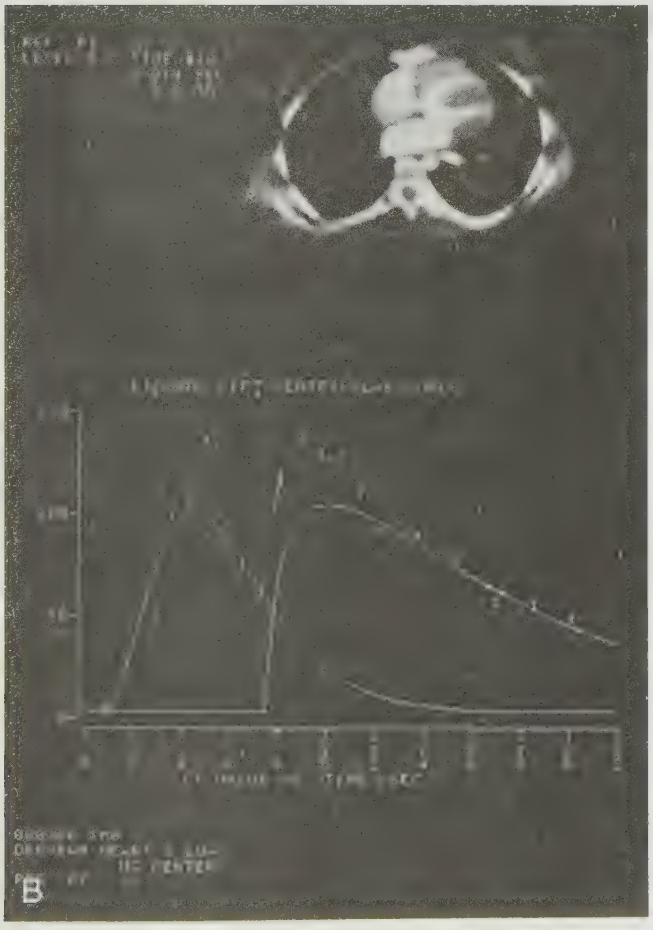


Fig. 52–23. Ventricular septal defect in a Cine-CT flow study with shunt calculation. (A) A Cine-CT flow study with 16 temporarily sequential images taken at the same level throughout one cardiac cycle. The injected contrast media courses through the heart beginning in the right atrium (A) and the right ventricle (V). The ventricular septal defect is visible, occupying approximately one-third of the length of the interventricular septum. (B) Time–density curves with cursor on the right ventricle disclosing a characteristic bimodal curve reflective of a shunt.

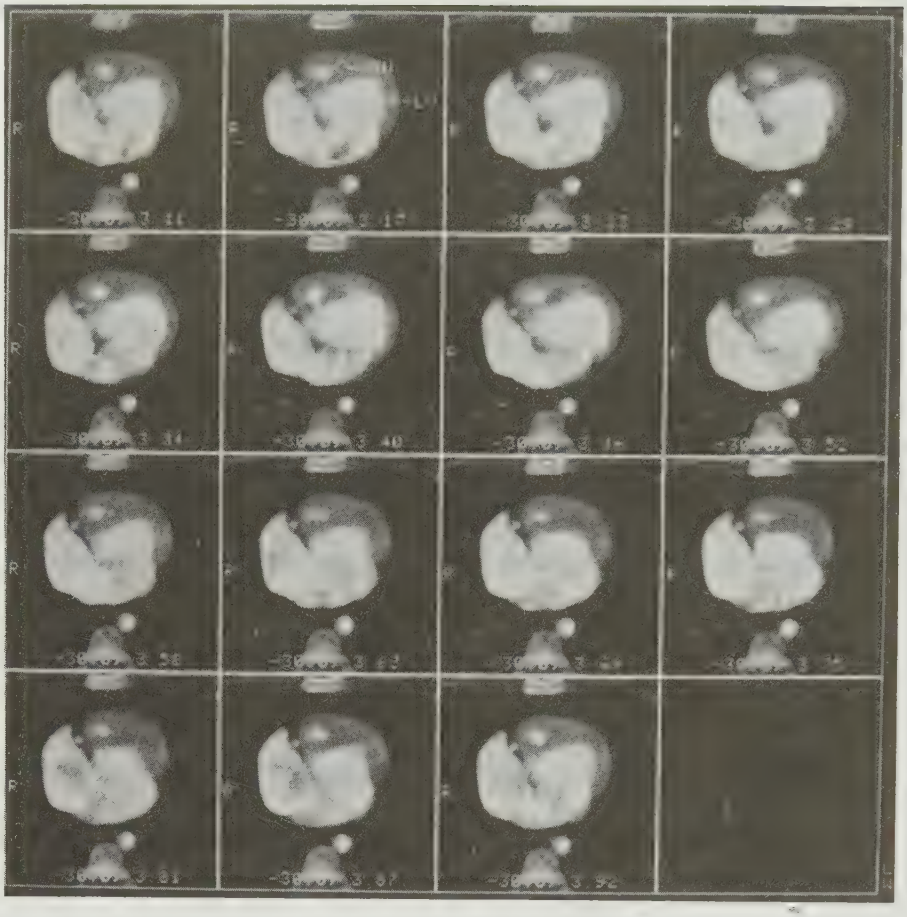


Fig. 52–24. A Cine-CT study of a young patient with hypoplastic right heart, atrial septal defect, and ventricular septal defect. The Cine mode is through the ventricles with a scan obtained every 58 ms (50 ms scan time and 8 ms interscan delay). Note the very small right ventricular cavity (RV) and moderate dilatation of the left ventricle (LV). Notice the thickening of the LV myocardium, especially at the LV apex level. (Courtesy of Imatron, Inc. and W.J. Eldredge and S. Flicker, Deborah Heart and Lung Center, Browns Mills, N.J.)

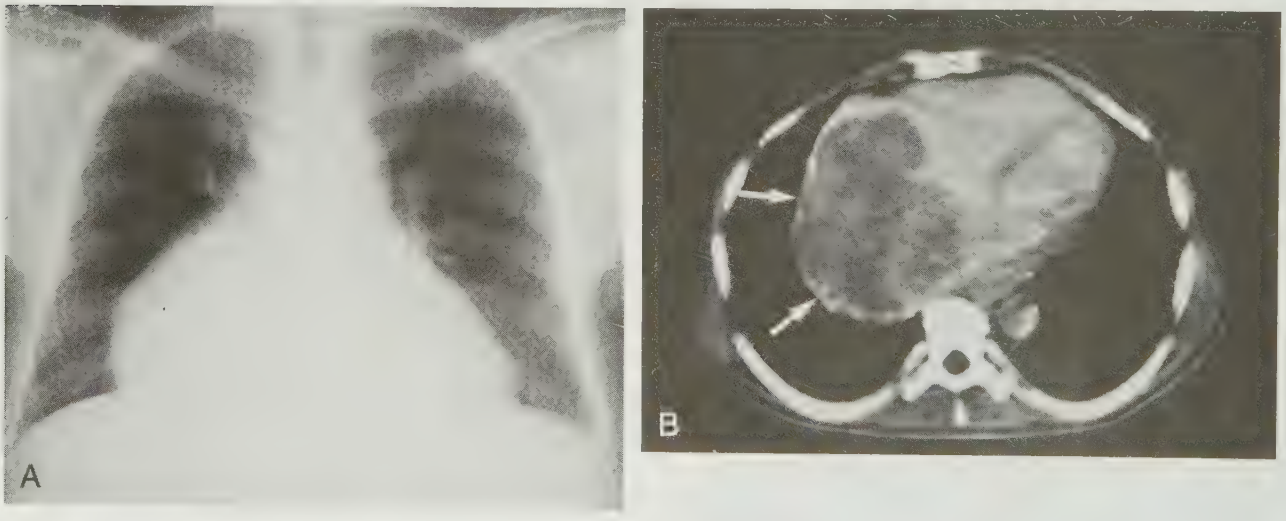


Fig. 52–25. A large right atrial tumor from hepatoma. This patient presented with malaise and an abnormal chest roentgenogram. (A) Chest film displays right atrial enlargement, possibly indicating Ebstein's anomaly, pericardial cyst, or right atrial tumor, perhaps a myxoma. (B) A CT scan discloses a large, primarily necrotic neoplasm (arrows) filling and expanding the right atrium. The right atrial wall cannot be separated from the mass, a feature raising the possibility of invasion.

Table 52–1. Anatomic Diagnoses

Diagnosis	*No. of Cases*
Aortic stenosis	5
Anomalous coronary artery	1
Atrial septal defect	22
Cardiomyopathies	10
Common atrium	1
Complete AV canal	8
Double-outlet right ventricle	3
d-transposition of the great vessels	10
Ebstein's anomaly	2
Hypoplastic right heart syndrome	4
l-transposition of the great vessels	4
Marfan's syndrome	2
Patent ductus arteriosus	4
Pulmonary atresia	13
Pulmonic stenosis	4
Single ventricle	19
Tetralogy of Fallot (preoperative)	15
Tetralogy of Fallot (postoperative)	11
Tricuspid atresia (preoperative)	6
Tricuspid atresia (postoperative)	2
Truncus arteriosus	1
Vascular ring	1
Ventricular septal defect	52

From Eldredge, W.J., and Flicker, S.: Evaluation of congenital heart disease using Cine-CT. Am. J. Card. Imag., *1*:38–50, 1987.

MRI are superior to conventional CT in these areas. Some congenital heart diseases such as septal defects can be diagnosed when dynamic scanning is used with the generation of time–density curves. Conventional CT can also detect Ebstein's anomaly and certain other configurational processes.

Cine-CT appears to offer a significant improvement over conventional CT and echocardiography in many congenital heart diseases.[19,21,24,48,49] Ebstein's anomaly (Fig. 52–22) and a variety of intracardiac shunt disorders including tetralogy of Fallot (Fig. 52–19), ventricular septal defects (Fig. 52–23), and atrial septal defects can be seen. Eldredge and Flicker[21] reported experience with over 200 patients with congenital heart disease studied with Cine-CT. A variety of lesions (Table 52–1) were seen in these patients, with Cine-CT making the correct diagnosis in over 90%. Cine-CT appears to be more accurate in the assessment of valvular disorders than conventional CT, though it is still probably not quite as sensitive as echocardiography.

Intracardiac shunts can be often demonstrated with Cine-CT and can be categorized by location. Calculations of the amount of shunt can also be performed by using time–density curve measurements and calculating the areas under the resulting bimodal curves.[17,26,37] In one study, Garrett and others created shunts between the main pulmonary artery and the left atrium in dogs. Cine-CT shunt calculations correlated well (r = 0.91) with oximetric values of 0 to 50%.[26]

Hypoplastic ventricular lesions are well seen with Cine-CT (Fig. 52–24). In experimental studies, Cine-CT more precisely defined the actual measurements of left ventricular and right ventricular casts than did biplane angiography.[51]

Physiologic evaluation of valvular disorders may also be possible with Cine-CT. In one experimental study, aortic insufficiency created by a basket was accurately assessed by Cine-CT compared with electromagnetic flow probes (r = 0.85).[52]

For intracardiac tumors and thrombi, CT is quite useful (Fig. 52–25).[27,37,53–57] In one study of 38 patients with CT and echocardiography,[56] CT displayed 22 intracardiac thrombotic lesions, while echocardiography identified only 6. The left atrium is particularly well seen with CT and poorly seen with echocardiography. Cine-CT likewise provides excellent anatomic details of intracardiac processes.

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UNIT 3

INVASIVE DIAGNOSTIC METHODS

CHAPTER 53

Digital Subtraction Angiography

William W Pinsky
David W Jones

In the 1970s, researchers in the field of digital subtraction angiography (DSA) believed that cardiac imaging would be revolutionized by this new technique.[1] Because of unrealistic expectations, software development disappointments, and the inability to archive acquired data efficiently, the acceptance of DSA has not been universal. It has been difficult for managers to justify the added expense of including DSA capabilities to an already expensive diagnostic laboratory.

Recent equipment developments, including more sophisticated software and archiving techniques, have made DSA a more attractive feature to cardiac catheterization laboratories. It is the purpose of this chapter to describe the past use of digital subtraction angiography in the cardiac catheterization laboratory, to outline the mechanics of applying this technique in a pediatric cardiac catheterization laboratory, to present examples of usage of DSA technique in pediatric patients, and to contrast cineangiography and DSA modes while also showing how they might complement each other.

CARDIAC APPLICATIONS

In many areas of medicine, advances first apply to adult before pediatric patients. This has been true in digital cardiac imaging. In contrast to the uses in pediatric patients, the adult cardiac lab has employed DSA more for understanding ventricular function, myocardial perfusion, and coronary artery stenosis than for imaging by itself.[2–6]

Initially, the basic difficulty in the use of DSA for cardiac work involved the motion of the heart during the cardiac cycle and the chest during respiration. The patient basically had to be motionless so that images could be subtracted from a previously selected mask. Also the contrast medium had to be delivered in a bolus large enough so that it could be concentrated properly. The motion problem was solved greatly by being able to add a different technique to the ''mask-mode'' method. In the previous method, one had to utilize a single image with no contrast, ''the mask'' and then ''subtract'' this from each subsequent frame. The new method, called time interval-difference (TID) imaging,[1] takes a series of images and integrates them (for more detail, see Chapter 39). This meant that during processing of an image, the masking could be performed repeatedly using several different images. This has helped to reduce motion artifact. The mask-mode and TID techniques are complementary. One can have a series of images from which a mask can be selected without exposing the patient to additional radiation. This discounts the effects of motion.

Having solved this problem, several investigators developed techniques to evaluate wall motion of the left ventricle.[4,5,7] Intravenous DSA does have the capability to verify the patency of saphenous vein grafts.[8] DSA systems with 512 × 512 matrices at rates of 15 to 30 frames per second can provide high-quality coronary images. This technique has the possibility of giving greater resolution than current cine technique. This also allows for ''road mapping'' (image freeze frame) for interventional angioplastic procedures. Another way to assess the effects of coronary artery disease using DSA is to measure myocardial perfusion.[6] By calculating the integral video density of the myocardium after contrast material has been injected into a coronary artery, the amount of contrast material that has entered the myocardium

can be estimated. One can calculate the arrival time of the bolus of contrast by video density.

On the other hand, up to now, pediatric application has been mostly in the imaging modes. Although intravenous DSA was first touted to be sufficient,[9] it actually requires intracavitary injections to obtain adequate imaging. Based on some initial imaging results in the adult patient aiding in the diagnosis of congenital heart disease, Levin in 1983 published a prospective study to investigate the diagnostic accuracy and potential benefits of DSA in a pediatric cardiac population. He and his associates performed DSA on 42 patients between the ages of 2 months and 18 years.[10] They compared this technique to conventional cine and cut film angiography. The DSA was performed utilizing a 512 × 512 matrix in single plane at 30 frames per second. Contrast injections for the intracardiac DSA ranged from 27.5 to 42% of the conventional dose. They demonstrated that the millirads received by the patients were only a fraction of that of either the cut film or cine. The diagnoses included shunt, obstructive, and regurgitant lesions. The authors felt that the diagnostic accuracy was at least equal to the other conventional techniques. Publications by other authors demonstrating congenital abnormalities of the aorta and aortic arch,[11] intracardiac masses,[11,12] anomalies associated with intracardiac left-to-right shunts,[9,13] aneurysms of the atrial, and ventricular septa,[13] all support Levin's findings.

Tonkin has a more recent publication with a larger series of pediatric patients utilizing intra-arterial injections.[14] She found that improved contrast resolution was obtained using smaller catheters and smaller amounts of contrast material compared to conventional imaging. The immediate availability of the images resulted in shorter total processing time. It was Dr. Tonkin's feeling that intra-arterial digital subtraction angiography eventually may indeed replace conventional imaging techniques.

TECHNIQUE OF DSA

Digital subtraction imaging is approached with the same goals and methods and basic methodology of conventional angiography. Since DSA is computer based, patient information can be inserted into the system prior to initiating the procedure. The DSA system can be preconfigured for the type of study, e.g., cardiac chamber, pulmonary artery, etc., and to select frame rate, radiographic settings, matrix site, and single or biplane views. The patient needs to be sedated to minimize motion. After the catheter is placed in the appropriate chamber and the appropriate position of the tubes is obtained, radiographic techniques should be checked to be sure that optimal energy settings are obtained. In most systems, once the DSA mode is selected, then fluoroscopy can be utilized as before, however, when the camera is activated, if the acquisition is then aborted, acquisition cannot be restarted until one resets the computer processing. It is extremely important that all "bright areas" (e.g., lungs) be shielded from x-ray exposure. Therefore, strict attention to "coning down" is necessary, supplemented by placement of bolus filters (radiopaque wedges) to cover transitional areas. Images are obtained and injections are performed just as during conventional imaging. Separate masking is not necessary. After acquiring the injection, one can choose a mask from the initial frames, which do not have contrast. Immediately following acquisition, the image is available for review. Compared to cine angiography, the image can be manipulated by various filtering and edge enhancement techniques to offer a better image. These are electronic mathematical manipulations that rearrange the digital information to reconstruct the image. On-line measurements of valves and arteries can be performed at this time to aid in interventional procedures. This is the ultimate goal of road mapping.

Following a procedure, the digital image can be manipulated further for contrast, brightness, and various temporal and spatial filters. The image can be reviewed on the hard disk console itself or transferred from the console to video tape format for later review. Hard copies are obtained utilizing either a laser or multiformat camera. Archiving is somewhat of a problem. One can imagine the amount of computer space needed to archive a 512 × 512 matrix at 30 frames per second in biplane in a typical pediatric case. The average cine length is 6 seconds and if an average of 2 injections per catheterization procedure are obtained, this requires quite a bit of disk space. For this reason, information needs to be compressed by deleting unnecessary or unwanted images and then transferring the material for more permanent storage on a device such as a magnetic tape recorder. This is similar to what is done in CT scanning.

In our laboratory we are currently able to obtain 512 × 512 10-bit matrices at 30 frames per second biplane. By utilizing biplane C-arms, complete oblique and long axial views are obtainable. The following examples (Figs. 53–1 through 53–6) show the type of detail that can be obtained in patients with tetralogy of Fallot, coarctation of the aorta, ventricular septal defect, interrupted aortic arch, and pulmonary atresia. These images have all been stored on magnetic tape as digital data so that more processing can be obtained at a later date.

We are able also to obtain various types of physiologic and anatomic information as demonstrated by Figure 53–7. Figure 53–7 was obtained from a patient who is after repair of anomalous origin of the left coronary artery. Automatic ventricular contouring is performed with subsequent ejection fraction calculated. Regional wall motion can also be viewed.

COMPARISON OF DSA TO CONVENTIONAL IMAGING

We believe that the above example shows that digital subtraction angiography imaging is at least equal to that of conventional techniques. Why therefore should one be willing to have the added cost to the laboratory to have DSA?

One obvious reason is that more information can be obtained with a single contrast injection. A lower total case dose of contrast medium therefore can be employed. This is a major advantage in pediatric cardiology. There is a dose-related toxicity associated with contrast medium, particularly in small infants. Large doses of contrast medium have been associated with rapid changes in acid–base balance, which can be detrimental to the cardiovascular system. In addition, osmolality changes also occur even with the newer isotonic mediums. Levin showed in his study that there is a marked reduction in radiation exposure to the patient as well as to the physician with digital subtraction angiography.[10] High doses of radiation are known potentially to be deleterious. Since many

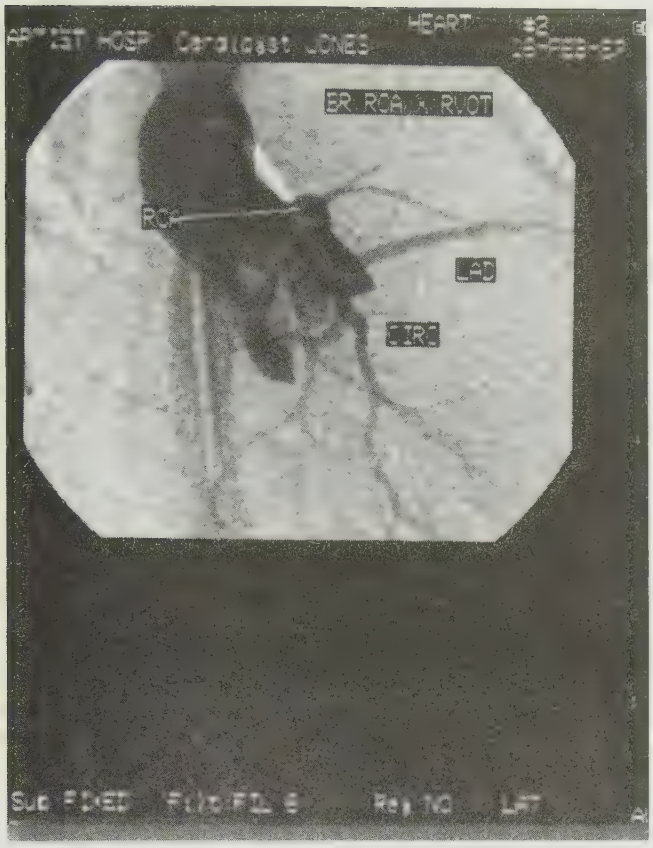

Fig. 53–1. Retrograde catheter in the ascending aorta with an injection to visualize coronary anatomy in a patient with tetralogy of Fallot. This angled view demonstrates great detail to the coronary circulation. RCA = right coronary artery; Br RCA × RVOT = branch of right coronary across the right ventricular outflow tract: LAD = left anterior descending coronary artery; CIRC = circumflex coronary artery.

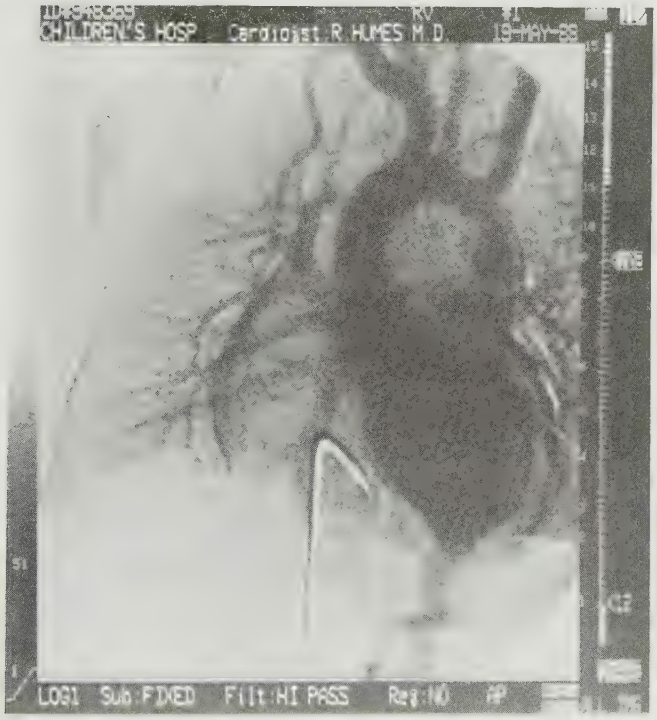

Fig. 53–2. This injection was obtained with the catheter in the right ventricle utilizing an angled view. The levophase of this injection demonstrates with great detail left ventricular and aortic anatomy. Note coarctation of the aorta and large collateral vessels.

Fig. 53–3. This is the levophase of Figure 53–2 utilizing the zoom function to better visualize the area of coarctation.

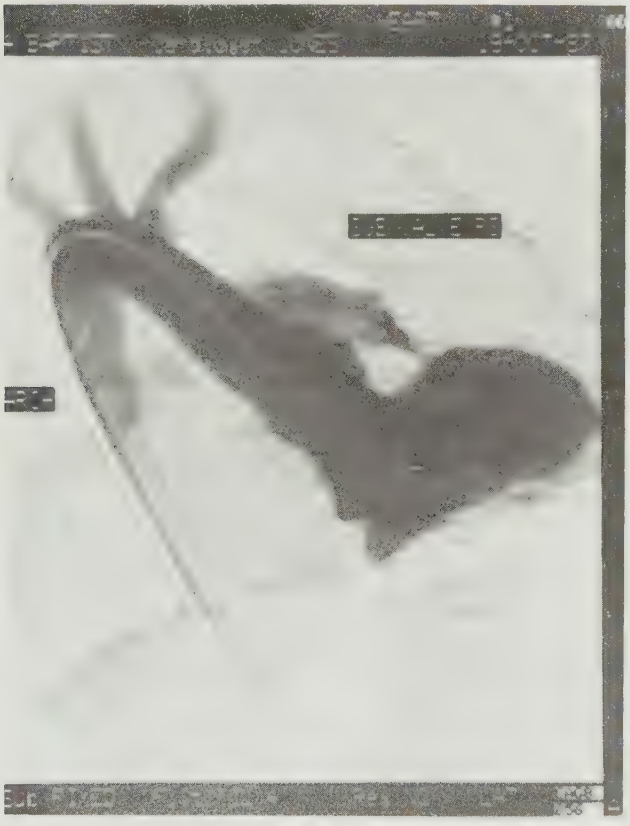

Fig. 53–4. The catheter is retrograde in the left ventricle. This angled view demonstrates a ventricular septal defect and marked subvalve pulmonary stenosis. LV = left ventricle; Arch = aortic arch.

Fig. 53–5. Straight AP view of a left ventricular injection in a patient with interrupted aortic arch and VSD. This injection demonstrates left-to-right shunting at the ventricular level and the interrupted aortic arch with collateral circulation. RSCA = right subclavian artery; LSCA = left subclavian artery.

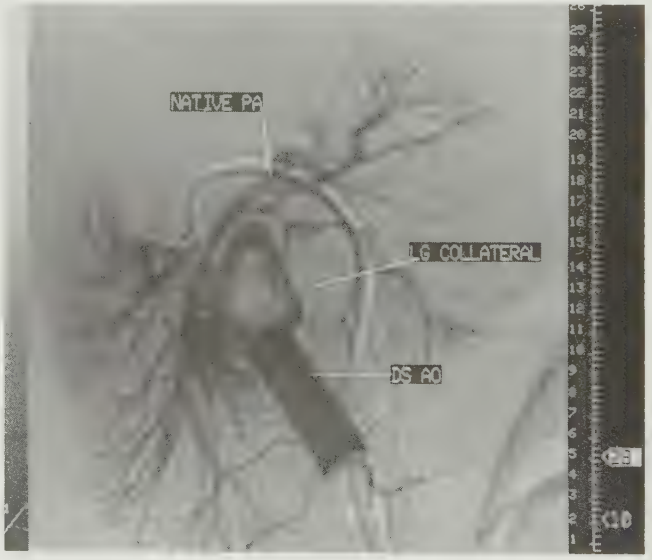

Fig. 53–6. Demonstration of utilization of DSA to visualize collateral arteries as well as small native pulmonary arteries in a patient with pulmonary atresia. DS AO = descending aorta.

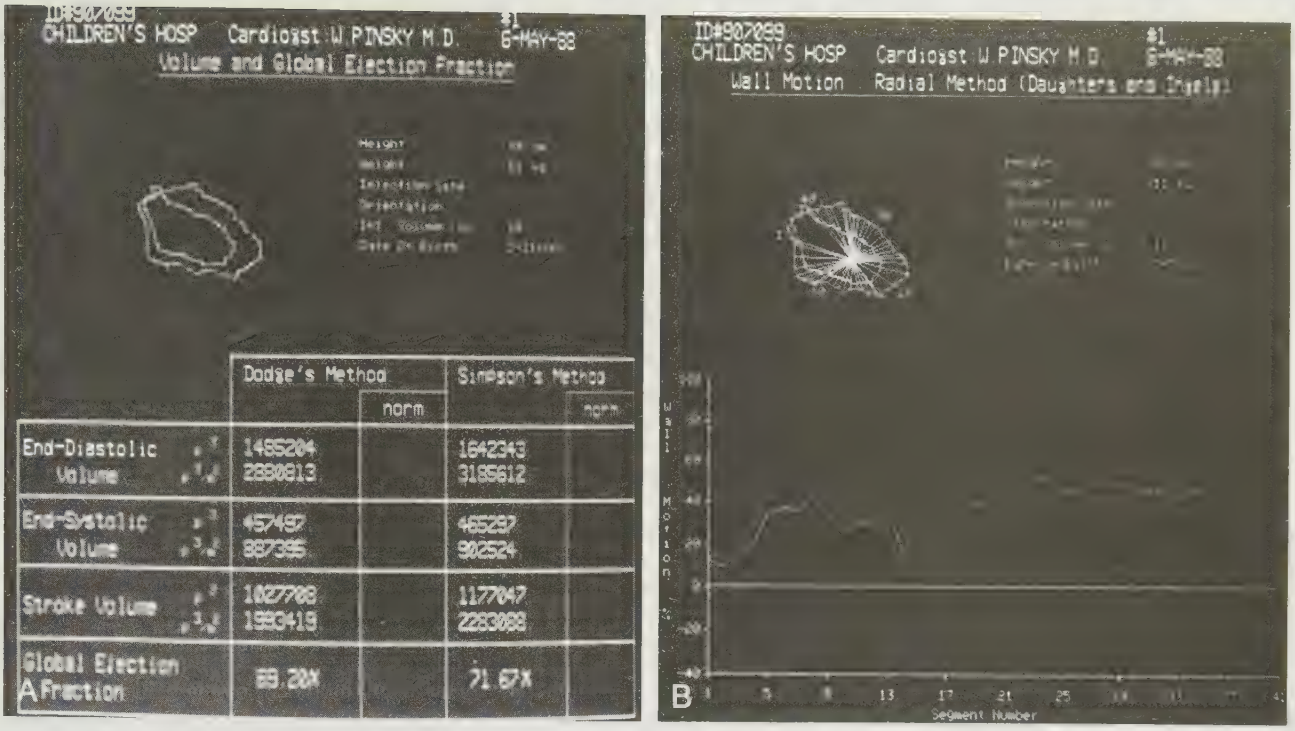

Fig. 53–7. Demonstration of on-line calculation function of DSA to generate ejection fraction from the global standpoint in (A) and in (B) utilizing the radial method to look for areas of localized wall motion abnormalities. This patient, after surgery to correct anomalous left coronary artery reimplantation, has areas of decreased motion in segments 14 and 15 as demonstrated by the graph in B.

pediatric patients undergo repeated cardiac catheterization their total radiation exposure generally is larger than in adults. Because smaller doses of contrast medium can be used, smaller catheters may be utilized. This is of benefit to reduce potential damage to the vascular access areas as well as to minimize intracardiac complications. Smaller doses of contrast medium for injection potentially will allow a greater number of injections when needed. Another advantage is the immediate availability of the images for review. This may shorten the procedure because of more firsthand knowledge of images acquired. Time in the catheterization laboratory is certainly related to morbidity.

FUTURE DEVELOPMENTS

Currently, digital subtraction angiography imaging is superb. Further advancements may be made in imaging as new filtering techniques are developed. There are basically mathematical applications to help with edge enhancement in particular.

Future advancements will be made in utilizing digital subtraction angiography to aid in the physiologic understanding of the lesions. This would include utilizing optical density for calculation of shunt size and regurgitant fractions, more accurate calculations of cardiac output, and volume calculations of chambers that do not fit the conventional geometric shapes utilized. For example, in postoperative Fontan patients, calculation of atrial size and function may aid in the understanding of postoperative hemodynamics.

Further development in digital data storage may also be able to improve the speed and efficiency of this technique. Even storing the data on magnetic tapes has its limiting factors. On the near horizon will be the ability to store digital information on tapes as small as those used for microcassette recorders. Optical disks are already available and may be an alternative to the magnetic tapes.

Whether or not digital subtraction angiography can supplant cineangiography remains to be seen. With improved efficiency and greater information content, DSA may assume an increasing role.

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CHAPTER 54

Cardiac Catheterization—Hemodynamic Measurements

Thomas A Vargo

This chapter is written primarily for the pediatric cardiologist who needs to learn basic hemodynamic principles and calculations. The chapter is not encyclopedic. The reader who wishes to learn more about a specific area may read one of the excellent textbooks or monographs devoted exclusively to cardiac catheterization.[1–5]

Throughout this chapter we have included historical background about hemodynamic measurements. We believe that this helps us accomplish two major goals: to understand which hemodynamic information and calculations are (were) important, and to understand how to use this information so that some of the data obtained at catheterization will be clinically relevant.

CARDIAC CATHETERIZATION—GENERAL COMMENTS

Almost all cardiac catheterizations in infants and children are performed with fluid-filled catheters. Blood sampling and angiography, important procedures in pediatric cardiac catheterizations, can only be done using fluid-filled catheters. Pressure recordings are not as accurate when obtained with fluid-filled catheters as they are when the pressure is recorded with microtransducer manometer–tipped catheters. However, manometer-tipped catheters are not suitable for use in most pediatric cases, as will be discussed later.

Catheters used for angiography usually do not have end holes and cannot be used for measuring pulmonary capillary wedge (PCW) pressures. In general, end-hole catheters are not used for angiography because of the increased likelihood of both intramyocardial staining and catheter recoil during injection through end-hole catheters. In sick children it is often advisable to use only one catheter, to allow the catheterization to be done as quickly and safely as possible. Thus, the physician must decide prior to the catheterization what information is to be obtained and which catheter or catheters should be used. For example, in a newborn with transposition of the great arteries (TGA) in whom a balloon atrial septostomy is to be performed, there is usually no reason to measure the PCW pressures, so there would be no reason to use an end-hole catheter.

If possible, the hemodynamic data should be obtained first, with an end-hole catheter. After this, the catheter is switched for an angiographic catheter. Contrast material will change the patient's steady state and alter the hemodynamic data. A suggested protocol for obtaining hemodynamic data is shown in Table 54–1. In children, there are times when it is neither possible nor practical to follow these guidelines. Intracardiac pressures, oxygen saturations, and cardiac output change dramatically whenever the child's steady state changes. These changes can occur if:

1. the patient awakens,
2. the patient requires sedation,
3. angiography is performed (for example, if one enters a chamber that may be difficult to re-enter later on, one should perform any necessary angiography before obtaining the remainder of the hemodynamic information; in complex congenital heart lesions, the general rule is "get whatever information you can while you are there, you may never be back"),
4. a significant amount of time is spent in entering various cardiac chambers in cases with unusual cardiac anatomy,

Table 54–1. Desired Sequence for Obtaining Pressure and Oxygen Saturation Data

Sequence	Pressures Recorded	Oxygen Saturation Obtained*
1. RPCW	Yes	No
2. RPCW→RPA	Yes	Yes
3. RPA→MPA	Yes	Yes
4. LPCW	Yes	No
5. LPCW→LPA	Yes	Yes
6. LPA→MPA→RVO	Yes	Yes
7. RVO→RVI	Yes	Yes
8. RVI→RA	Yes	No
9. LIV	No	Yes
10. SVC	No	Yes
11. RA high	No	Yes
12. RA low	No	Yes
13. IVC	No	Yes
14. LV	Yes	Yes
15. LA	Yes	Yes
16. RPV	Yes	Yes
17. LPV	Yes	Yes
18. LA→RA	Yes	No

Abbreviations: RPCW and LPCW = right pulmonary and left pulmonary artery capillary wedge positions; RPA, LPA and MPA = right, left, main pulmonary arteries; RVO and RVI = right ventricle below the pulmonic valve and right ventricular body, respectively; LIV = left innominate vein; SVC and IVC = superior vena cava and inferior vena cava; RA and LA = right atrium and left atrium; LV = left ventricle; RPV and LPV = right and left sided pulmonary veins; → = catheter withdrawal pressure recordings.

*Oxygen saturations are only obtained at the end of a pressure withdrawal recording.

The above suggested sequence must be modified depending upon the patient's cardiac lesion. If possible, we usually begin our recordings of pressure and oxygen saturations in the PCW position as it is usually quicker to withdraw the catheter from the pulmonary artery to the other cardiac chambers than to begin in the atria and push the catheter forward into the various cardiac chambers. We begin in the PCW position that is first obtained, if the left PCW position was obtained first, withdrawal tracing would start there. Each pressure recording is obtained at a scale which fills the entire paper while continuing to show the entire pressure curve. A simultaneous systolic arterial pressure (usually femoral artery) is simultaneously recorded whenever the pressure is measured in the MPA, RV and LV. A femoral artery oxygen saturation is obtained at the beginning and end of this sequence of obtaining hemodynamic data. Systolic and diastolic pressures are measured in all arteries and ventricles. Mean pressures are measured in the wedge positions, both atria, all arteries, and the pulmonary veins. "a" and "v" waves are measured in the wedge positions and in both atria.

5. one is not able to enter the left side of the heart from a prograde venous catheterization.

All these factors can alter the patient's cardiovascular status enough to invalidate the hemodynamic information obtained.

We prefer to use woven Dacron catheters because we find them to be easy to manipulate, to retain their shape well, to give reasonably accurate pressure records, and to be excellent angiographic catheters. However, one's experience should dictate which types of catheter he or she uses for cardiac catheterization. We believe the ability to do "skilled purposeful catheterizations" is being lost by the popularity of balloon-flotation catheters. There are times when the nonfloating, standard catheters are preferable. Thus, we disagree with the statement in an excellent textbook that "abnormal positions of the heart chambers and of the great vessels associated with cardiac dilatation or with congenital malformation present difficulties even to experienced laboratory cardiologists" and that "these problems have been largely overcome by the introduction of balloon-tipped flow-directed catheters. . . ."[6]

For example, balloon catheters usually do "float" easily into the pulmonary artery of most patients, but in patients with either a massively dilated right ventricle (RV) or severe regurgitation of the tricuspid or pulmonary valve it is frequently impossible to enter the pulmonary artery with a balloon catheter. We find in these cases that it is much easier to enter the pulmonary artery with a large bore standard catheter that is appropriately curved, as these catheters are not "pushed back" by the valvular regurgitation as are the soft balloon catheters.

However, since the balloon-tipped flow-directed catheter is the catheter most commonly used in pediatric patients, we will mention some of our recommendations about the use of these catheters. Carbon dioxide should always be used to inflate the ballon whenever there is a possibility that rupture of the balloon would result in gas embolism to the systemic circulation. In our opinion, this includes all children with congenital heart lesions, as the catheter will often be manipulated into the systemic circulation, even in patients who are thought to have neither a right-to-left shunt nor any other communication between the venous and systemic circulations. Some physicians forget to flush the catheter with carbon dioxide (CO_2) prior to its use, not realizing that the lumen contains air and has a volume which is about one quarter the size of the inflated balloon. Because of possible bacterial contamination in the CO_2, the CO_2 should be filtered with a 0.22-micron filter prior to its use for balloon inflation. When such a catheter is inserted into the circulation to obtain blood samples, the single end hole of the "wedge catheters" will frequently be stuck against a vascular wall or the side of the heart; in most cases minimal inflation of the ballon will free the catheter tip and permit a blood sample to be obtained.

A balloon-flotation catheter is advantageous because 1) it is simple to use, 2) it is relatively safe, especially in babies (in whom the majority of cardiac perforations occur), 3) the pulmonary artery can be entered relatively quickly in children with TGA, 4) in patients with an inter-atrial communication, the aorta can often be entered from the left ventricle (LV) rather than having to perform a retrograde catheterization, 5) wedge pressures are usually easily obtained, 6) in patients with ventricular inversion (corrected TGA) complete AV block is usually less common when using balloon catheters to enter the pulmonary artery, 7) less skill and training are needed to use such catheters, 8) angiography catheters with inflated balloons have less chance of causing intramyocardial extravasations of contrast, and 9) angiography balloon-tipped catheters can be "pushed" into the ventricles, causing less chance of recoil of the catheter into the atrium during injection of contrast material.

One disadvantage of balloon-flotation catheters is that the angiographic catheters allow injection of only relatively small volumes of contrast material. These catheters sometimes should not be used when large volumes are needed such as for ventriculography in children with large left-to-right shunts.

Balloon catheters can cause rupture of the pulmonary artery, especially if they are inflated while positioned distally in a branch of the pulmonary artery.[7,8] As mentioned, rupture of the balloon

can also cause air and bacterial emboli, although this will usually not cause damage if filtered CO_2 has been used.

PRESSURE DATA

Pressure measurements are the most important of the hemodynamic data obtained during cardiac catheterization. Elevated pressure due to stenosis of a valve is the main determinant of whether valvular surgery (or balloon dilation) is performed. Pulmonary hypertension often determines whether surgery is recommended in patients with left-to-right shunts. A difference in atrial pressures is one of the reasons for performing atrial septostomy in children in whom blood flow must cross the atrial septum, such as those with TGA, total anomalous pulmonary venous return, and mitral atresia.

The pressure of a cardiac chamber could be measured by connecting the catheter to a tall glass tube filled with fluid. Since the LV pressure in aortic stenosis could be 200 mm Hg or greater, this would require a tube of water at least 8 feet, 11 inches tall. Obviously this is not practical, and pressures are measured instead with transducers, which are discussed in Chapter 30. Tall glass tubes also cannot be used to measure the rapidly changing cardiac phasic pressures because the fluid level moves too slowly. Instead, the pressure inside a tall thin glass tube would be closer to the average or mean pressure in that cardiac chamber. Again, since tall tubes are not practical, mean pressures are now calculated electronically. While phasic pressures should be obtained from every cardiac chamber, mean pressures are obtained only in the veins, arteries, and atria. Mean pressures are used for the calculation of vascular resistances, which will be discussed later.

Before starting the catheterization, the pressure transducer is placed at the level of the heart and is opened to air; the pressure recorder is then calibrated so it will read "0" at atmospheric pressure. This is known as the zero reference point and means that a fluid-filled catheter exposed to atmospheric pressure will read 0 mm Hg when its tip is at the same level as the transducer. In pediatric cases, the level of the transducer, or the zero reference point, is set at the midchest position in the supine patient. In children, the midchest level is essentially at the level of the entrance of the superior vena cava (SVC) and inferior vena cava (IVC) into the right atrium. In adults there are at least six different positions where the transducer can be placed for setting the zero reference point, all of which are attempts to try to have the transducer set at the same level as the heart.[9]

For a correct reading the transducer must be at the same level as tip of the catheter, or the pressures will be incorrect depending on the difference between the height of the transducer and the catheter tip. If the tip of a fluid-filled catheter is elevated above the transducer, there will be a positive pressure of 1 mm Hg for each 1.36 cm of elevation above the zero reference point (mercury is 13.6 times denser than water). Similarly, a negative or reduced pressure will be recorded if the catheter tip is below the level of the transducer. For example, if the tip of the catheter is 4 cm lower than the transducer, the pressure will be 3 mm Hg lower than if the catheter tip and transducer were at the same level.

It would be preferable to change the level of the transducer to the level of the catheter tip with each pressure measurement, but this is not practical as the differences in pressures during cardiac catheterization in children are usually only 1 to 2 mm Hg from the true zero reference point. This difference is insignificant in measuring ventricular systolic, pulmonary, and aortic pressures. However, an improper zero reference point can materially change the atrial and ventricular diastolic pressure measurements; this is especially true in adults and large children, who have a much greater anteroposterior (AP) chest diameter than do babies, whose AP diameter is only about 10 cm.

To obtain accurate pressure measurements, the catheter, all tubing and stopcocks, the transducer, and the recording system (taken as a whole unit) should reliably reproduce the actual pressure curve. This requires that there is no amplitude distortion of any of the sine wave frequencies that make up the pressure curve. A cardiac pressure curve (according to my simplification of Fourier analysis) is the sum of all its sine wave frequencies, from the lowest frequency, which is the heart rate, up through its maximum frequency, which is 10 times the heart rate. To illustrate this, at a heart rate of 120 beats per minute, the frequency is 2 cycles per second, or 2 Hz; in order to get an accurate reproduction of the pressure curve at this heart rate the entire catheter–tubing–transducer–recorder system must not have any amplitude distortion of any of the sine wave frequencies from 2 through 20 Hz. At a heart rate of 180 beats per minute, there should not be any frequency distortion up to 30 Hz. The larger the bore of the catheter, the stiffer the catheter, the shorter the tubing, and the fewer stopcocks, the better the frequency response will usually be. For most pediatric catheterizations, the catheter–transducer–recorder systems should have a nondistorted frequency response up to 10 to 30 Hz. In practicality, it is only in babies, who have fast heart rates and in whom smaller catheters are used, that a relatively poor frequency response causes problems in pressure measurement during routine cardiac catheterization.

Despite meticulous calibration, whenever two catheters are used for simultaneous pressure recordings, the tracings are rarely the same. Because of this, it is often better to perform a withdrawal tracing (e.g., from the LV to the aorta) than two simultaneous tracings, even though simultaneous tracings do make it easier to compare pressure gradients. Whenever two catheters are used, one should make sure that the transducers provide similar data by switching the tubing between the two catheters to confirm that both transducers result in identical pressure curves. Another way to confirm that the readings are correct is to place the two catheters in the same cardiac chamber, in which case the pressure tracings should be equal and be superimposed on each other.

If pressures appear to be erroneous, the catheter–tubing–transducer–recorder system should be checked and recalibrated. Causes of falsely low pressures include a clot or loose connection in the catheter or catheter system, a kinked catheter, entrapment of the catheter in a portion of the heart (usually in ventricular muscle), and air bubbles in the tubing or transducer not allowing transmission of the pressure wave. On the other hand, if entrapment forces the catheter against a blood vessel wall, a falsely high pressure can be recorded. Air bubbles can also create standing waves, which increase the amplification of the pressure wave causing an exaggerated overshoot on the initial portions of both the systolic and diastolic ventricular pressures.

Manometer-tipped catheters should be used when exact pressure measurements are required. Even though the pressure curves with manometer-tipped catheters are superior, these catheters are rarely used in children because of their disadvantages:

1. They are fragile and expensive.
2. They require delicate zeroing and calibration.
3. They "drift" easily after calibration.
4. They are relatively stiff.
5. The smallest catheter with side holes for performing angiography is size 7F.
6. The flow rate (and therefore the volume) that can be injected is limited compared to standard catheters (10–15 mL/sec for a 7F manometer-tipped catheter).

As shown in Figure 54–1, there is not much difference between the pressure recorded with a manometer-tipped catheter and a fluid-filled one.[10] Thus, with the disadvantages just listed there is not much reason to use these catheters in children. The two main abnormalities in the pressure recordings obtained with the fluid-filled catheters are the "overshoot" and the delay of about 30 to 40 msec for the pressure wave to be transmitted to the transducer. The major reasons for using manometer-tipped catheters are for research applications, where, for example, by using two manometers on the same catheter, precise gradients can be determined.

The positioning and direction of the catheter can affect the pressure measurement.

1. Catheters will read lower pressures when they are in an area with higher velocity of the blood flow (Bernoulli effect). For example, the pressure in a narrow segment of a stenotic pulmonary artery branch can be lower than the pressure downstream, where the pulmonary artery is of normal size.
2. If the tip of the catheter or one of its openings is in the atrium but lying against the mitral or tricuspid valve, catheter impact artifact during opening or closing of the atrioventricular valve can give a strikingly tall but artifactually elevated atrial wave, which can be confused with an abnormal "a," "c," or "v" wave.
3. Because forward flow can convert kinetic energy into pressure, end-hole catheters generally add 2 to 4 mm Hg when facing the flow of blood, and subtract 2 to 3 mm Hg when they are in the direction of the flow. In some cases, it is possible for a femoral or brachial arterial line facing the flow to have the pressure 10 mm Hg higher than if the line faced downstream.
4. The motion of the catheter in the beating heart along with fluid acceleration may produce superimposed waves of as high as 7 to 10 mm Hg. This is called catheter whip artifact and seems to be particularly common in the pulmonary artery, where artifactual superimposition of systolic readings can be as great as 10 mm Hg.

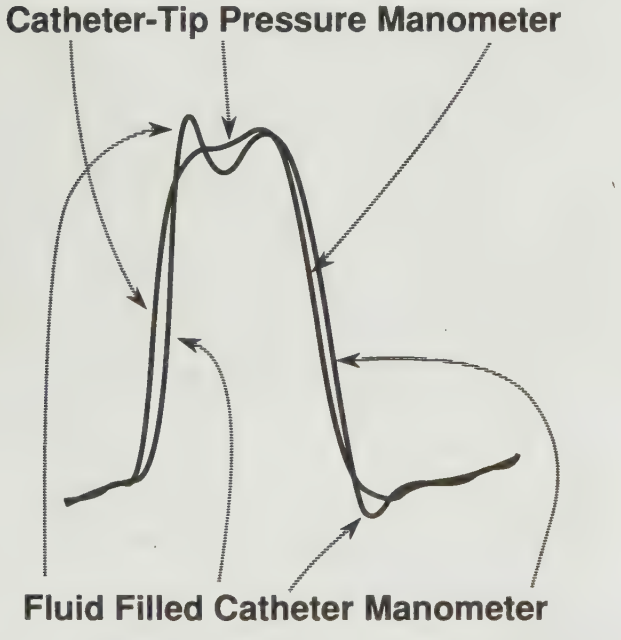


Fig. 54–1. Comparison of pressure recordings between a fluid-filled catheter and a manometer-tipped catheter. Note the similarities of these simultaneous left ventricular pressure records obtained with the catheter-tip pressure manometer and with a fluid-filled catheter. The main "errors" with the fluid-filled system are the "overshoot" at the beginning of systole, the "undershoot" at the beginning of diastole and the delay in the pressure response of the catheters. (Reproduced with permission from Cardiovasc. Res., *12*:566, 1978.)

In essence, the heart beats inside a "mild vacuum." Normal intrathoracic pressure is about 0 to 8 mm Hg less than atmospheric pressure. Thus, part of the atrial pressures and the early diastolic pressures in the ventricles often are less than "zero" or atmospheric pressure (less than the "zero reference point"). Dehydration, crying, and hyperpnea can be associated with intracardiac pressures well below the zero reference point. The right atrium especially can have subatmospheric pressures. Therefore, it is possible for air to be introduced into the right atrium if the catheter is disconnected from either the transducer or its tubing. Whenever we disconnect a catheter with its tip in the atrium, we keep the catheter hub at a low enough level that blood flows backwards from it. Raising the catheter hub can introduce air, which could then be flushed into the body when the catheter is connected back to the flushing system. Large amounts of air can be introduced into the right atrium if the femoral vein sheath is not kept occluded whenever the catheter inside it is withdrawn or exchanged.

Normal pressure measurements in children during cardiac catheterization are listed in Table 54–2.[11–13] This information is essentially "old" data; it was based primarily on children who had a normal heart. Younger cardiologists may not remember that

Table 54–2. Normal Intracardiac Pressures in Children (in mmHg)

	Average	*Range*
Right atrial mean	1–4	−3 to 8
Right ventricular, systolic	24–29	13–42
Right ventricular, end diastolic	3–5	0–10
Pulmonary arterial, systolic	20–22	11–36
Pulmonary arterial, diastolic	7–10	3–21
Pulmonary arterial, mean	11–12	6–22
Pulmonary arterial wedge or left atrial, mean	6–9	2–14
Left ventricular, systolic	100–106	72–133
Left ventricular, diastolic	7–10	3–14
Systemic arterial, systolic	108	77–150
Systemic arterial, diastolic	61–64	50–83
Systemic arterial, mean	70–81	67–105

These values are derived from references 11, 12 and 13. The author believes that the average values are reasonable, but that often the ranges listed are greater than what usually occurs in normal children.

before echocardiography, cardiac catheterization was frequently performed in children with functional murmurs who turned out to have normal hearts.

Pulmonary Capillary Wedge Pressure

Pulmonary capillary wedge pressures are used to estimate the pulmonary venous and left atrial pressures. The mean PCW pressure is usually close to the mean left atrial pressure, with the PCW pressure usually 1 mm Hg higher than the left atrial pressure.[14–16] The PCW pressure is attenuated compared to the left atrial pressure and the "c" wave is usually not seen. Differences in the level of the catheter tip can cause a 5 to 7 mm Hg difference in wedge pressures between a posterior pulmonary segment and an anterior pulmonary segment.[17] In our experience PCW pressures in the same patient are within 2 mm Hg of each other.

For calculating pulmonary vascular resistance, direct measurement of the pulmonary venous pressure or the left atrial pressure is preferable to estimating it from the PCW pressure. However, entering the left atrium is not always possible, and even if a left atrial pressure is obtained, the pulmonary veins may not be entered. In patients with lesions such as cor triatriatum, the PCW pressure may be the only way to estimate the pulmonary venous pressure. Except for those who are exceedingly skilled with the transseptal technique, it may not be desirable to enter the left atrium in certain patients, such as those who have had a Mustard operation or those who have had a large patch closure of an ostium primum atrial septal defect.

The transmission of the phasic contour waveform from the left atrium to the wedge pressure is usually delayed by 20 to 100 msec, depending on the length from the tip of the catheter to the transducer as well as on the type and diameter of the tubing used.[3,9,16]

Infrequently, we have seen abnormally elevated or low pressures in the pulmonary wedge position from forcing the catheter too vigorously into the wedge position; presumably this is because the catheter tip is forced against a blood vessel wall. In these cases the pressure is attenuated and withdrawing the catheter slightly will usually give a typical phasic PCW tracing.

In many cases it is difficult to tell if the catheter is completely wedged or not, as the pressure contour will seem to be somewhere in between a typical pulmonary artery and a PCW pressure. In addition, in patients with a large pulmonary blood flow, it is often difficult to "wedge" the catheter. Furthermore, in patients with large shunts there is a watershed effect of pressures flowing from the PCW position to the pulmonary vein to the left atrium, and the PCW pressure will be higher than the left atrial pressure.[18] To determine whether the catheter is truly wedged, one should withdraw the catheter on a continuous pressure tracing. If the catheter is wedged, the pressure will usually increase suddenly to a typical pulmonary artery pressure curve and the catheter will tug when it is released from the wedge position. If a good "tug" is not felt, the catheter may not have been wedged. One can demonstrate that the catheter is wedged if aspirated blood has 95% arterial saturation. We rarely do this because it often takes so long to obtain a PCW blood sample that clot formation will occlude the catheter.

Pulmonary Artery Pressure

The diastolic pressure of the pulmonary artery (PA) is usually 1 to 3 mm Hg higher than the mean PCW pressure. The PA systolic pressure should be about the same as the right ventricular pressure. The dicrotic notch represents closure of the pulmonic valve in the beginning of diastole.

Pulmonary artery pressures will vary depending on whether an end-hole or a side-hole catheter is used. As previously discussed, end-hole catheters frequently read a different pressure than side-hole catheters, depending on velocity of flow and the direction the catheter is facing (it is possible for it to be facing the flow of the pulmonary artery if the catheter enters the pulmonary artery through a surgical shunt anastomosis or a patent ductus arteriosus). Occasionally, the pressure will be higher in a pulmonary artery branch than in the main pulmonary artery, usually the left pulmonary artery.

If there is a large ventricular septal defect or ductus arteriosus, the pulmonary artery systolic pressure equals the aortic systolic pressure because there is no restriction of pressure from the left side to the right side of the heart. In patients with a large ventricular shunt, the greater the volume of pulmonary blood flow, the lower the diastolic and mean pulmonary artery pressures will be compared to the aortic diastolic and mean pressures. Obviously, since the systolic pressures are equal, the pulse pressure in the pulmonary artery will also be greater than that in the aorta.

Sometimes it is impossible to obtain a typical pulmonary artery pressure curve in patients who have an exceedingly tight pulmonary artery band or severe branch stenosis. In these cases, if the catheter can even be manipulated across the narrow area it may completely occlude the lumen and one will obtain a PCW pressure rather than a pulmonary artery pressure.

Right Ventricular Pressure

After the pulmonary artery pressure is recorded, the catheter should be withdrawn slowly into the right ventricle (RV) to determine whether there is a gradient across the pulmonic valve. After obtaining the right ventricular outflow tract pressure the catheter is withdrawn from just below the pulmonic valve to the body of the RV to see if there is a subvalvular gradient. When withdrawing the catheter from the pulmonary artery, the catheter tip should be kept pointed in a cephalad direction (by continued clockwise torque). Otherwise, the catheter will usually "drop" from the pulmonary artery into the body of the RV, in which case one would be unable to tell from a pressure tracing whether any gradient present was due to valvular or subvalvular obstruction. If precise determination of the outflow tract gradient is needed, then an end-hole, double-lumen, or manometer-tipped catheter must be used. Usually this is not necessary because even if the withdrawal tracing is poor, determination of the location of the stenosis is best demonstrated by angiography.

When premature ventricular contractions (PVCs) are induced by mechanical stimulation with the catheter, the pressure response can frequently be used to tell whether or not the patient with right ventricular hypertension has pulmonary stenosis or a large ventricular septal defect (VSD). If there is a large VSD, the right ventricular systolic pressure will remain equal to the aortic and left ventricular systolic pressure after the PVC. If there is pulmonic stenosis without a VSD, the RV pressure will increase significantly during the post-PVC beat; this is because there is usually a significantly increased stroke volume following a PVC, and all the extra blood must cross the pulmonic valve. Also, in pulmonic stenosis without a VSD, the pressure curve during right ventricular

contraction and relaxation is similar to an isosceles triangle, with a narrow base and relatively tall equal sides.

Right ventricular diastolic pressure is essentially equal to simultaneous right atrial pressures. Diastole begins at approximately "0" mm Hg (the zero reference point), rises slowly, and has a peak, due to atrial contraction, just before systole begins. The end-diastolic pressure of the RV is usually the nadir of the pressure wave that occurs after the atrial "a" wave. As in the left ventricle, it is questionable whether early diastolic pressure ("end systolic") should be recorded or not. We believe that it should. Congestive heart failure, restrictive cardiomyopathy, and pericardial constriction can cause all diastolic pressures to be elevated (including the early diastolic pressure). However, others assume that the early diastolic pressure should be close to the zero reference point and that only the end-diastolic pressure needs to be measured.

Right Atrial Pressure

The right atrial pressure is obtained on a withdrawal tracing from the RV to the right atrium (RA). The atrial pressure consists of "a," "c," and "v" waves. The "a" wave corresponds to atrial systole and is the first wave after the "P" wave of the ECG. The "c" wave is the deflection that occurs in early systole and corresponds to tricuspid valve closure. It is not clinically useful in pediatric cardiology. The "v" wave reflects filling of the atrium in late systole against the closed atrioventricular valve. In the RA the "a" wave is usually greater than the "v" wave by about 2 to 3 mm Hg. The "v" wave reaches its peak just before the tricuspid valve opens. There is a large "v" wave if tricuspid regurgitation is present. The "x" descent is the descending pressure that occurs after the "a" wave. The "x" descent continues to fall even after the tricuspid valve closes due to continued relaxation of the right atrium along with descent of the atrioventricular ring during ventricular systole. The "y" descent is the decreasing pressure which occurs after the "v" wave and is due to opening of the tricuspid valve. In normal individuals, right atrial pressure is essentially identical to pericardial pressure.[19]

By convention, pressures are taken at end expiration if respiration is quiet. The pressure in the RA can be less than atmospheric pressure and in inspiration may be as much as 7 to 9 mm Hg less than atmospheric pressure, especially if the patient is crying. Airway diseases cause the greatest fluctuations in pressure in the right atrium because of the marked changes in intrathoracic pressure during respiration.

Left Ventricular and Arterial Pressures

Systemic arterial and left ventricular (LV) pressures should be obtained simultaneously. Femoral and brachial arterial systolic pressures are usually 7 to 15 mm Hg greater than the LV pressure, and may be as much as 30 mm Hg greater.[17,20] Femoral artery diastolic pressure is usually lower than central aortic pressure by 2–6 mm Hg. Thus, if the femoral artery systolic pressure is 5 mm Hg less than the peak LV systolic pressure, the actual peak systolic gradient across the aortic valve would be approximately 15 mm Hg. The elevated systolic pressures in the peripheral arteries appear to be due to pulse amplification as the pressure waves are reflected back from arterial branch points, including the bifurcation of the abdominal aorta.[21]

There are many causes of an abnormally low incisura or dicrotic notch. In general, the causes are all associated with a large stroke volume. The greater the LV output, the wider the pulse pressure and the lower the diastolic pressure and dicrotic notch. In pediatric patients, the most common causes of an increased LV output are surgical systemic to pulmonary arterial shunts, patent ductus arteriosus (PDA), aortic regurgitation, anemia, fever, and exercise. Severe aortic stenosis, on the other hand, can cause a narrow pulse pressure with a wave on the ascending limb of the pressure tracing (known as an anacrotic notch) present on the ascending portion of the pressure curve. The LV pressure curve will have an isosceles triangular shape in aortic stenosis, but not as much as occurs with pulmonic stenosis.

Left ventricular diastolic pressures are similar to right ventricular diastolic pressures though LV pressures are higher, partially because of the greater wall thickness of the left ventricle and reduced compliance compared to the RV. Exactly where to determine the end diastolic pressure, in either the LV or the RV, is sometimes difficult to determine. With simultaneous atrial and ventricular pressure recordings, it is easy to determine the end diastolic pressure because it is at the point just before systole where the left atrial and LV pressure curves cross each other. Without simultaneous pressure recordings, the exact location of the end diastolic pressure is more difficult to determine. With a single pressure curve, the end diastolic pressure is usually at the nadir of the ventricular diastolic pressure, which occurs after the pressure wave due to the transmitted atrial "a" wave.

Left Atrial Pressure

In the left atrium (LA) the "v" wave is the dominant wave rather than the "a" wave. The "v" wave is related to pulmonary blood flow and is increased when pulmonary blood flow is increased, such as in a VSD with left-to-right shunting. The "v" wave is also partially due to pulmonary venous contraction. If ever there is a question of mitral stenosis, simultaneous left ventricular diastolic and PCW or LA pressures should be obtained. With mitral stenosis, the LA can usually only be entered using the transseptal technique, and therefore often only one catheter is inserted into the LV and the LA. If there is mitral stenosis, there is a gradient between the "a" wave and the LV end diastolic pressure. Mitral regurgitation causes an accentuated "v" wave.

We have developed a technique of measuring simultaneous left-sided pressures with the transseptal technique (Fig. 54–2). The LV pressure is measured with a catheter that is smaller than the lumen of the transseptal sheath. LA pressure is measured via a side arm connected to the sheath. Using this method requires meticulous attention to flushing and other technical details to ensure that clots and air bubbles are neither introduced into nor allowed to form within the sheath. After the LV and LA pressures are recorded, we confirm that the pressure records from the sheath and catheter are identical by withdrawing the LV catheter into the LA to make sure that the two pressures do superimpose. In order to obtain simultaneous and withdrawal pressures in the aorta, LV and LA, we often "float" a balloon catheter into the aorta from the sheath and then begin a series of catheter and sheath withdrawals, as demonstrated in Figure 54–2.

After LA pressures are obtained, the catheter is withdrawn from the LA to the RA, with LA pressure usually two to three times greater than RA pressure. In the presence of a large atrial septal defect, the atrial pressures are usually equal; however, equal pressures do not guarantee a large communication since the right atrial

Fig. 54–2. Example of three simultaneous pressures: patient with subaortic stenosis and coarctation (numbers on side of tracing are pressures in mm Hg). The pressure in the left ventricular inflow (LV in) area is measured using a Mullins transseptal sheath. A fluid-filled catheter inside the sheath is withdrawn from the ascending aorta (Asc Ao) to the LV outflow (LV out) position. The gradients across the subaortic area and coarctation are confirmed by systolic pressures of approximately 75 mm Hg in the femoral artery (FA), 105 mm Hg in the Asc Ao, 140 mm Hg in the LV out, and 200 mm Hg in the LV in. In this tracing there is about an 80 msec delay between the upstroke of the Asc Ao and FA pressures. Also note on the right side of the tracing that the LV in and the LV out diastolic pressures exactly coincide. Later in this case we pulled the tip of the transseptal sheath into the left atrium on a "higher gain" and noted no diastolic gradient across the mitral valve (thus, no mitral stenosis).

pressure may be elevated for another reason, e.g., Ebstein's disease, tricuspid atresia, or postoperative tetralogy of Fallot. However, if the pressures are significantly different and all the blood flow has crossed an atrial septal defect (ASD) in either direction (such as in mitral atresia, tricuspid atresia, or total anomalous pulmonary venous return), then the pressure difference confirms that blood flow is restricted.

Pulmonary Venous Wedge Pressure

There are cases where one is unable to measure the pulmonary artery (PA) pressure directly. PA pressures can be estimated by pulmonary venous wedge pressures which are assessed by wedging the catheter into a pulmonary vein. At that time, the pressure curve will resemble a PA pressure curve.

Wedged pulmonary venous pressures correlate with PA pressures.[22] If the mean pulmonary vein wedge pressure is less than 19 mm Hg, then the mean PA pressure is low and is usually less than 20 mm Hg. If the mean pulmonary vein wedge pressure is greater than 19 mm Hg, then the PA pressure is usually elevated, often with significant PA hypertension.

Pulmonary venous wedge pressures used to be the only way to estimate PA pressure in many cases of either TGA or pulmonary atresia. The development of balloon flotation catheters has made it possible to enter the PA in most cases of TGA. It is also frequently possible to enter the PA in children in whom the only blood flow to the lungs is by way of a shunt anastomosis. In those rare cases when this is not possible, pulmonary venous wedge pressures should be assessed.

OXIMETRY

This section discusses oximetry, which is the measurement of oxygen saturation of hemoglobin in a sample of blood. However, we will also use the term *oximetry* to mean any measurement of oxygen in the blood, especially when these measurements are important in calculating cardiac hemodynamics.

Oxygen saturation is the proportion of oxygen combined to hemoglobin divided by the oxygen capacity, and is described by the formula:

$$O_2 \text{ saturation} = \frac{(O_2 \text{ content} - \text{dissolved } O_2) \times 100}{O_2 \text{ capacity}}$$

The *oxygen content* is the total amount of oxygen present in a blood sample. It is a combination of the oxygen bound to hemoglobin plus the *dissolved oxygen*. The latter is the amount of oxygen dissolved in the plasma. The *oxygen capacity* is the theoretical maximal amount of oxygen that can be taken up by the hemoglobin. The oxygen capacity (in mL O_2/L) can also be calculated by multiplying the hemoglobin (in g/dL) by 13.6. This is because each gram of hemoglobin in a liter of blood will combine with 13.6 mL of oxygen when the hemoglobin is fully (100%) saturated.[23,24]

Early in the history of cardiac catheterization, oximetry was the primary means of diagnosing an intracardiac shunt. The detection of small shunts was not possible by oximetry, primarily because the determination required relatively large volumes of blood and there was a time delay before the oximetry result was available. Shunts less than 30 to 50% of the total cardiac output could not be detected by these older and relatively insensitive oximetry methods. Thus, to this day, the misconception persists that a shunt can only be definitely diagnosed by a "step up" or increase in oxygen saturation of 3 to 7% (Table 54–3). With present-day techniques, small shunts can be detected by oximetry. However, these shunts are usually currently diagnosed by echocardiography or cineangiography.

In current practice, oxygen saturation values can be repeated quickly (5 to 20 sec to obtain a reading), using small volumes (0.1 to 0.5 mL) for each specimen. Because of this, we can now diagnose much smaller shunts, as shown by the following extreme example. If one took 100 blood samples in the pulmonary artery and they all had an 80% oxygen saturation, while 100 samples in the right ventricle had a 79% saturation, then the patient would almost certainly have a very small left-to-right shunt into the pulmonary artery. Multiple samples are also used to help locate a shunt. For example, if a patient has one pulmonary vein entering the superior vena cava, one can sample repeatedly until the area

Table 54–3. Oximetric Detection of Intracardiac Shunts by Percent Increase or Decrease in Saturation

Cardiac Chambers Sampled	*One Sample*	*Multiple Samples*
Superior vena cava and right atrium	7%	5%
Right atrium and right ventricle	5%	3%
Right ventricle and pulmonary artery	4%	3%
Left atrium or pulmonary vein and left ventricle or systemic artery	−3%	−2%

Increases (step up) in oxygen saturation samples between two cardiac chambers which are diagnostic of the presence of a left-to-right shunt in the distal chamber. We believe that a "step down" from the left atrium or pulmonary vein to the left ventricle or systemic artery of −3 to −2% is necessary to diagnose a right-to-left shunt. References 25–28.

of the elevated saturation is localized and then usually probe with the catheter to enter the abnormally draining pulmonary vein.[25–28]

Oximetric values also have an important role in calculating the magnitude of a shunt and determining whether surgery is necessary. A pulmonary-to-systemic flow ratio of greater than 2.0:1 usually indicates a large left-to-right shunt and a defect that should be surgically closed just because of the volume of the shunt. Furthermore, right-to-left shunting and the amount of systemic desaturation often determines when to perform surgery in patients with cyanotic congenital heart lesions.

When pediatric heart catheterization became a "routine" procedure in the 1950s, oxygen contents were measured by the Van Slyke technique and other manometric methods.[29] These methods required 15 to 30 minutes to obtain a reading; they were technically difficult to perform, and required significant expertise to get a correct reading. While the Van Slyke method is the standard for oximetric determinations, most pediatric laboratories now use the spectrophotometric method to determine oxygen saturation.[30,31] Spectrophotometry is based on Beer's law, which states that "the absorption of light by a solution is a function of the concentration of its solute(s) and the depth of the solution." The absorption coefficients for light transmission of oxyhemoglobin and desaturated hemoglobin can be measured at two different wavelengths, and the difference in the amount of light absorbed is proportional to the concentration of each form of hemoglobin. From this difference in absorption, the concentration of oxyhemoglobin and desaturated hemoglobin are determined, and thus the oxygen saturation can be computed.

In the red range (630 to 660 nm), the light transmission of oxyhemoglobin and desaturated hemoglobin are different, while in the infrared (770 nm and above) and green (510 nm) range the transmissions are similar. One type of modern spectrophotometer measures in the red and infrared ranges at wavelengths of 670 nm and 930 nm. Oxyhemoglobin is measured in the red range and total hemoglobin in the infrared range. Other spectrophotometers measure in the green and red range. We have not found that one type is better than the other.

The spectrophotometric method is quick, accurate, precise, does not require using heparinized syringes, and is subject to few errors. Most errors in spectrophotometry are due to substances in the blood that interfere with light absorption. Spectrophotometric readings will be inaccurate if large amounts of carboxyhemoglobin are present, but usually this will only cause inaccuracies if it is present in significant concentrations, as in heavy smokers. Also, indocyanine green causes interference with the light source of many spectrophotometers, because it has a spectral absorbency in the range of 700 to 850 nm with peak absorbency at 800 to 810 nm. Thus, green dye curves should preferably be done after the oximetry has been done. Elevated bilirubin levels can also affect the absorption of spectrophotometric methods.

Spectrophotometry has about 1% error at 95% oxygen saturation and about 2.5% error at 70% saturation. It is relatively accurate to values of 40 to 50% saturation; spectrophotometric oximetry is not reliable at saturations lower than this. However, at such low values, precise determination of saturations is not usually necessary because it is obvious that something "must be wrong" with the patient, and the calculation of hemodynamic data in these cases is usually not important. If necessary, saturations below 50% can be determined by the blood gas method.

The next most common way to determine oxygen saturation in pediatric catheterization laboratories is by calculating the saturation from the oxygen dissociation curve (Fig. 54–3). The calculation of the saturation from the dissociation curve depends on the affinity of oxygen for hemoglobin, which depends on multiple factors including the temperature, pH, P_{CO_2}, and amount of fetal hemoglobin. The advantage of the blood gas method is that oxygen content can be calculated, which is important in those breathing high concentrations of oxygen. Like most laboratories we routinely use spectrophotometry and usually only obtain blood gases during the catheterization to confirm that a simultaneous oxygen saturation is the same as by spectrophotometry.

We attempt to begin the catheterization by obtaining oximetric and pressure measurements in rapid sequence, as outlined in Table 54–1. In many cases we can obtain all the saturations and pressures in 5 minutes or less. In our experience it is more rapid to begin in the PCW position than in the SVC position (because time can be spent getting to the PA and PCW). Obviously, the less time it takes to obtain the data, the more likely that the child will remain in a steady state during the hemodynamic portion of the catheterization.

Shunts can cause inaccurate readings themselves, as demonstrated by the following examples. Pulmonary artery oxygen saturations will be elevated if the blood sample is taken from an area where a ductus arteriosus or aortopulmonary anastomosis is directing its jet of fully saturated blood into the sampling catheter. On the other hand, one will not obtain a true pulmonary artery oxygen saturation if the collateral supply to the lungs is distal to the point where the sample was taken. The right ventricular outflow tract (and even the proximal pulmonary artery) may have an abnormally elevated saturation if the sampling location is in the stream of a VSD. We routinely sample in the left innominate vein because we have found many cases of unsuspected left-to-right shunts due to partial anomalous pulmonary venous return from the left upper lung into this vein. In such a case, the oxygen

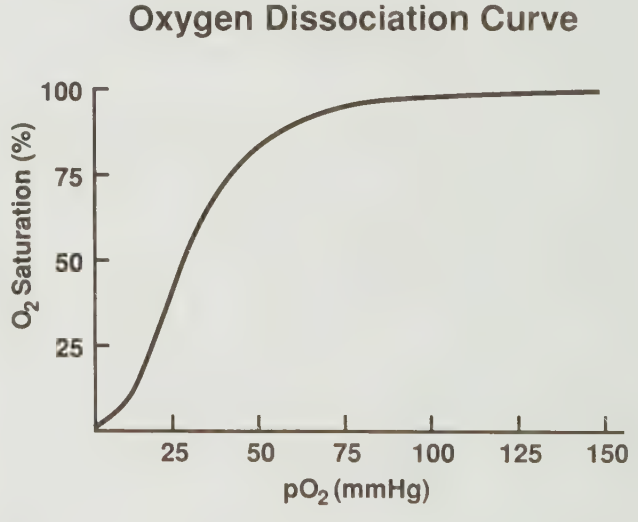


Fig. 54–3. Oxygen dissociation curve: this curve can be used to determine how much dissolved oxygen (pO_2) is present at given oxygen saturation (O_2 sat) and vice versa. At pO_2 values above 150 mm Hg, assume that the O_2 sat is essentially 100%.

saturation in the SVC will be higher than in the "true" mixed venous blood.

There are two major problems in oximetry. Namely, what is the definition of "mixed venous blood," and how to determine what it is when there is a left-to-right shunt? The *mixed venous blood* is the sum of all of the blood leaving the systemic vascular bed, which then enters the heart. Because of streaming from all the veins entering the heart, complete mixing (and a true average) of the blood does not occur until blood enters the pulmonary artery. Thus, the pulmonary artery oxygen saturation is used for the mixed venous blood sample in patients without a shunt. However, the pulmonary artery saturation cannot be used when there is a left-to-right shunt because the pulmonary artery contains both the mixed venous blood plus the blood from the shunt.

In patients who have left-to-right shunts it is often difficult to determine what the average oxygen saturation is in the venous blood proximal to the shunt, especially if there is an ASD. This is because the blood entering the right atrium is, in essence, coming from eight different veins: the coronary sinus, the SVC, the azygous vein, the IVC, two hepatic veins, and two renal veins, and the saturations differ markedly from each of these veins.

If there is a left-to-right shunt there are many different methods used to attempt to determine the mixed venous blood oxygen saturation. Most of these involve various combinations of SVC and IVC blood samples.[32] However, the saturation of the SVC approximates the pulmonary artery saturation closely enough that we routinely use only the SVC saturation for the mixed venous saturation (except when there is a proximal shunt, such as supracardiac total anomalous pulmonary venous drainage).[33] SVC saturations are often erroneously high if one inadvertently samples from the azygous vein instead.[34]

We routinely obtain an IVC saturation (below the hepatics); however, there is marked normal variation in this value. While the patient is awake and breathing room air the saturation in the IVC is higher than in the SVC; the reverse occurs in patients receiving general anesthesia.[35] Another reason for not using the IVC samples for oximetry is that barely moving the catheter will cause significant differences in oxygen saturations. The greatest streamlining and variation of oxygen saturations occurs in the area of the IVC and right atrial junction. Samples obtained close to the coronary sinus may have saturations as low as 25 to 40%, while saturations obtained from the renal veins may be greater than 90%[36]; saturations from the two hepatic veins will be between the coronary sinus and renal vein sample values, and may vary significantly from the remainder of the IVC blood flow.

For qualitatively detecting an intracardiac shunt by oximetry all that is needed is to have a significant "step-up" of oxygen saturation in the right heart or a "step-down" in the left heart. However, to measure the volume of a shunt, one needs to know the oxygen consumption and the oxygen saturations in the pulmonary artery, the pulmonary veins, a systemic artery, and the SVC (we use the SVC saturation for the mixed venous saturation, as discussed). The saturations in the PA, pulmonary vein (PV), and systemic artery (SA) do not have nearly as many potential errors as does the mixed venous (MV) saturation. We will now discuss how to quantitate intracardiac shunts and blood flow by oximetry. Several formulas for this calculation are shown in Table 54–4.

Qp is the amount of blood flowing through the pulmonary capillary bed (pulmonary flow), and Qs is the amount of blood flowing through the systemic capillaries (systemic flow). A left-to-right shunt is the amount of oxygenated blood that bypasses the systemic vascular bed. A right-to-left shunt is the amount of desaturated blood that bypasses the pulmonary vascular bed. Qep (effective pulmonary flow) is the quantity of mixed venous blood that carries desaturated blood from the systemic capillaries to be oxygenated by the lungs. It is equal to the quantity of pulmonary venous blood that carries oxygenated blood from the lungs to the systemic capillaries. Qp/Qs is the ratio of pulmonary blood flow to systemic blood flow; it is always calculated so that the denominator is 1; Qp/Qs is the only one of these formulas that does not require the oxygen consumption for its calculation.

Table 54–4. Formula for Calculating Blood Flow Using Oximetric Data

$$Qp = \frac{VO_2}{PVO_2 - PAO_2} = \frac{VO_2}{(PVsat - PAsat)\ (O_2\ capacity)}$$

$$Qs = \frac{VO_2}{SAO_2 - MVO_2} = \frac{VO_2}{(SAsat - MVsat)\ (O_2\ capacity)}$$

$$Qep = \frac{VO_2}{PVO_2 - MVO_2} = \frac{VO_2}{(PVsat - MVsat)\ (O_2\ capacity)}$$

$$QP/QS = \frac{SAsat - MVsat}{PVsat - PAsat}$$

Left-to-right shunt = Qp − Qep

Right-to-left shunt = Qs − Qep

Net shunt = (left-to-right shunt) − (right-to-left shunt)

O_2 capacity = 13.6 × gm hgb/dL

Abbreviations: VO_2 = oxygen consumption. PVO_2, PAO_2, SAO_2, and MVO_2 = O_2 content of the pulmonary veins, pulmonary arteries, systemic arteries, and mixed venous blood, respectively. PVsat, PAsat, SAsat, and MVsat represent pulmonary vein, pulmonary artery, systemic artery and mixed venous O_2 saturations, respectively. Qp = pulmonary blood flow, Qs = systemic blood flow which is the cardiac output, Qep = the effective pulmonary blood flow.

All blood flows are measured in liters of blood flowing per minute, as the units of VO_2 are mL of O_2 consumed per minute and the units of O_2 content are mL of O_2 per liter of blood. In this chapter O_2 content is measured in ml O_2/L of blood rather than ml O_2/dL of blood, as is done in many other texts. The O_2 content of blood contains both dissolved O_2 and the O_2 combined with hemoglobin. While breathing room air the amount of O_2 dissolved in the blood is insignificant compared to the amount of O_2 combined with hemoglobin, and dissolved O_2 is not used for the calculation of blood flows. Frequently, Qp/Qs is the primary means of diagnosing the magnitude of an intracardiac shunt. If one compares the complete formulae for Qp and Qs one can see that VO_2 and O_2 capacity cancel out so that only the systemic artery, mixed venous, pulmonary vein and pulmonary artery saturations are needed to calculate the ratio of pulmonary to systemic blood flow.

The terms Qp, Qs, Qep, left-to-right shunt, and right-to-left shunt are best explained by a series of box diagrams and examples of calculations. Oxygen consumption (VO_2) will be discussed in the next section; in order to perform the calculations in these examples, it is necessary to use arbitrary values for VO_2. In the first three examples the hemoglobin is 13 g/dL, the O_2 capacity is 176.8 mL O_2/L, and the VO_2 is 88.4 mL O_2/min.

Example 1 (Fig. 54–4). A patient with a VSD has aortic and

pulmonary vein oxygen saturations of 96%, a pulmonary artery saturation of 86%, and an SVC saturation of 76%. In this case one should be able to deduce that the amount of mixed venous blood returning to the lungs is equal to the volume of the left-to-right shunt, because the pulmonary artery saturation of 86% is exactly midway between the mixed venous saturation of 76% and the aortic saturation of 96%. The calculations in this case are:

$$Qp = \frac{88.4}{(0.96 - 0.86)176.8} = 5 \text{ L/min}$$

$$Qs = \frac{88.4}{(0.96 - 0.76)176.8} = 2.5 \text{ L/min}$$

$$Qep = \frac{88.4}{(0.96 - 0.76)176.8} = 2.5 \text{ L/min}$$

$$\text{Left-to-right shunt} = 5 - 2.5 = 2.5 \text{ L/min}$$

The left-to-right shunt is equal to the Qep; thus, total blood flow through the pulmonary circulation is twice the systemic flow (Qp/Qs = 2/1). It is obvious that Qp is a combination of blood returning to the lungs from the body plus the left-to-right shunt.

Example 2 (Fig. 54–5). Assume that the previous patient had a pulmonary artery band placed and that the VO_2, hemoglobin, and O_2 capacity remain the same. However, the patient now has only a right-to-left shunt without a left-to-right shunt. For calculation purposes the pulmonary vein oxygen saturation is 95%, the aortic saturation 85%, and the mixed venous and pulmonary artery saturations are both 70%. The following calculations apply:

$$Qp = \frac{88.4}{(0.95 - 0.70)176.8} = 2 \text{ L/min}$$

$$Qs = \frac{88.4}{(0.85 - 0.70)176.8} = 3.3 \text{ L/min}$$

$$Qep = \frac{88.4}{(0.95 - 0.70)176.8} = 2 \text{ L/min}$$

$$\text{Right-to-left shunt} = 3.3 - 2.0 = 1.3 \text{ L/min}$$

Because of the right-to-left shunt, the blood flow through the lungs has to be less than the blood flow through the body. Thus:

$$Qp/Qs = \frac{2}{3.3} = 0.6/1$$

As always, the amount of blood flowing through a vascular bed is the Qep plus any blood shunted back to that vascular bed.

Example 3 (Fig. 54–6). Imagine that the band is not quite as constricting and there is bidirectional shunting with a pulmonary vein oxygen saturation of 97%, aortic saturation of 90%, pulmonary artery saturation of 86%, and SVC saturation of 66%. Again, assume the same VO_2 and O_2:

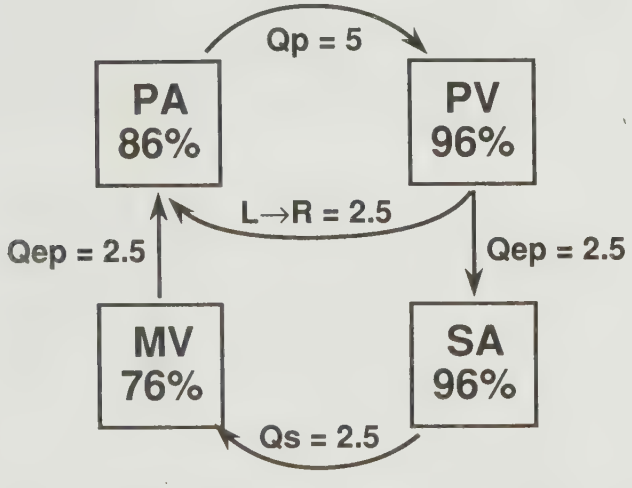


Fig. 54–4. Example 1, diagram of a left-to-right shunt: in these and the next few similar diagrams the boxes represent the pulmonary artery (PA), pulmonary vein (PV), aorta (Ao) or systemic artery (SA), and mixed venous (MV) or superior vena cava (SVC). Each box contains the values for the oxygen saturations obtained in each location. In these diagrams, aorta and systemic artery are used interchangeably, as are superior vena cava and mixed venous. The arrows represent the blood flow from one "box" (or cardiac chamber) to the next in liters per minute. See Example 1 in the text for further explanation. See Table 54–4 for explanation of Qp, Qs, left-to-right (L→R) shunt, etc. For making the diagrams simpler to understand, the word "shunt" is left out of "L→R shunt" (and "R→L shunt").

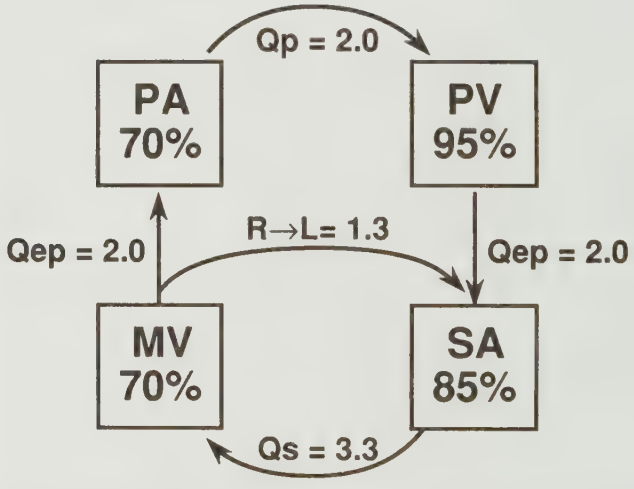


Fig. 54–5. Example 2, diagram of right-to-left shunt: see Figure 54–4 and text for further explanation.

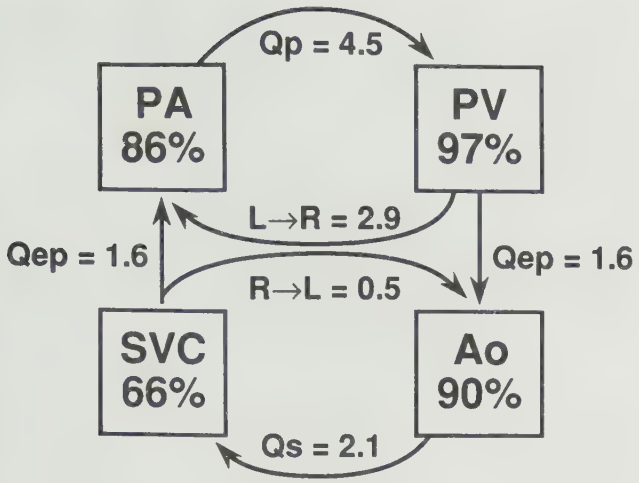


Fig. 54–6. Example 3, a bidirectional intracardiac shunt: see Figure 54–4 and text for further explanation.

Thus,

$$Qp = \frac{88.4}{(0.97 - 0.86)176.8} = 4.5 \text{ L/min}$$

$$Qs = \frac{88.4}{(0.90 - 0.66)176.8} = 2.1 \text{ L/min}$$

$$Qep = \frac{88.4}{(0.97 - 0.66)(176.8)} = 1.6 \text{ L/min}$$

$$\text{Left-to-right shunt} = 4.5 - 1.6 = 2.9 \text{ L/min}$$

$$\text{Right-to-left shunt} = 2.1 - 1.6 = 0.5 \text{ L/min}$$

$$\text{Net shunt} = 2.9 - 0.5 = 2.4 \text{ L/min}$$

$$Qp/Qs = \frac{4.5}{2.1} = 2.14/1$$

As is always true, the Qep remains the same on both sides of the diagram, because the amount of mixed venous blood going to the lungs to be oxygenated is equal to the amount of pulmonary venous blood that delivers oxygen to the tissues.

Note that in the first three examples the Qp/Qs can be determined without calculating Qp or Qs, nor is the VO_2 or O_2 capacity required. This will be true *whenever the patient is breathing room air* because only the oxygen saturations are needed for the calculations, as VO_2 and O_2 capacity cancel out:

$$\frac{Qp}{Qs} = \frac{\dfrac{VO_2}{(PV - PA \text{ sat})\ (O_2 \text{ capacity})}}{\dfrac{VO_2}{(Ao - MV \text{ sat})\ (O_2 \text{ capacity})}} = \frac{Ao - MV \text{ sat}}{PV - PA \text{ sat}}$$

Thus, for Example 1: $\dfrac{Qp}{Qs} = \dfrac{96 - 76}{96 - 86} = 2/1$

For Example 2: $\dfrac{Qp}{Qs} = \dfrac{85 - 70}{95 - 70} = 0.6/1$

For Example 3: $\dfrac{Qp}{Qs} = \dfrac{90 - 66}{97 - 86} =$ 2.18/1 (a slight difference due to rounding off)

In our opinion, the formula for "net shunt" (which is the difference between the left-to-right shunt and the right-to-left shunt—see Table 54–4 for calculation) is a meaningless number, but it is sometimes used in older literature. To emphasize this point, a patient could have a massive left-to-right shunt of 5 L/min with a similar massive right-to-left shunt of 5 L/min and the net shunt would be 0. However, in such a case there would obviously be very abnormal hemodynamics—in actuality, this situation does occur in patients with TGA.

The formulas used and the description of blood flow in TGA is the same as for any other lesion. Desaturated blood that returns to the systemic circulation is a right-to-left shunt, oxygenated blood that returns to the lungs is a left-to-right shunt, and so on. Representative values for oxygen saturation in a patient with TGA are 96% in the pulmonary veins, 88% in the pulmonary artery, 69% in the aorta, and 50% in the SVC. Patients with TGA usually have hemoglobin values higher than in the previous three examples, so that for this example (Fig. 54–7) we will make the hemoglobin 18 g/dL, the O_2 content 244.8 mL O_2/L, and the VO_2 122.4 mL O_2/min. The following calculations apply to this patient with TGA.

$$Qp = \frac{122.4}{(0.96 - 0.88)244.8} = 6.25 \text{ L/min}$$

$$Qs = \frac{122.4}{(0.69 - 0.50)244.8} = 2.6 \text{ L/min}$$

$$Qep = \frac{122.4}{(0.96 - 0.50)244.8} = 1.1 \text{ L/min}$$

$$\text{Left-to-right shunt} = 6.25 - 1.1 = 5.15 \text{ L/min}$$

$$\text{Right-to-left shunt} = 2.6 - 1.1 = 1.5 \text{ L/min}$$

The diagram in Figure 54–7 looks the same as the previous three diagrams. However, it can be seen that the right-to-left and the left-to-right shunts are much larger than the Qep.

The box diagrams in Figure 54–8 better demonstrate the anatomy and hemodynamics of TGA, as they demonstrate the aorta receiving the desaturated blood from the vena cava and the pulmonary artery receiving oxygenated blood from the pulmonary veins. Figure 54–8 demonstrates that the so-called "parallel circulation" of blood that occurs in TGA is due to the significant right-to-left and left-to-right shunts.

It is apparent from Figure 54–8 that if a patient with TGA had an ASD and no other defect, the only way blood could go from the lungs to the body (and vice versa) would have to be through the ASD. In TGA the blood flowing across the ASD is, in essence, normal blood flow. That is to say, this is how the oxygenated

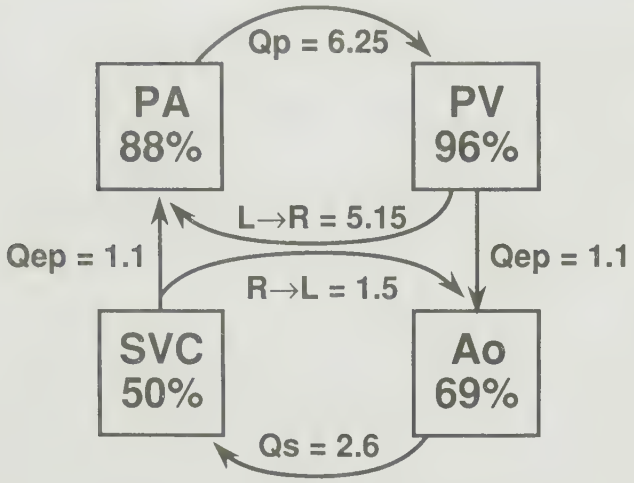


Fig. 54–7. Example of bidirectional shunting in transposition of the great arteries: see Figure 54–4 and text for further explanation.

blood reaches the body, and the desaturated blood reaches the lungs. Hemodynamically, blood flowing from the left atrium to the right atrium in TGA is not a left-to-right shunt, but is the Qep; similarly, the blood flowing from the right atrium to the left atrium in TGA is not a right-to-left shunt but is the Qep.

Finally, in TGA the amount of blood flowing from the lungs to the body has to equal the amount of blood flowing from the body to the lungs. While this is obvious in this example of TGA, it is also true in every person, or all the blood would eventually be in either the pulmonary vascular bed or the systemic vascular bed.

Is it important to include the dissolved oxygen in calculating pulmonary blood flow? While breathing room air the answer is "no," as the amount of dissolved oxygen is usually only about 1% of the amount of oxygen combined with the hemoglobin. However, while breathing oxygen the answer is often "yes," as the volume of dissolved oxygen is much larger, as will now be demonstrated.

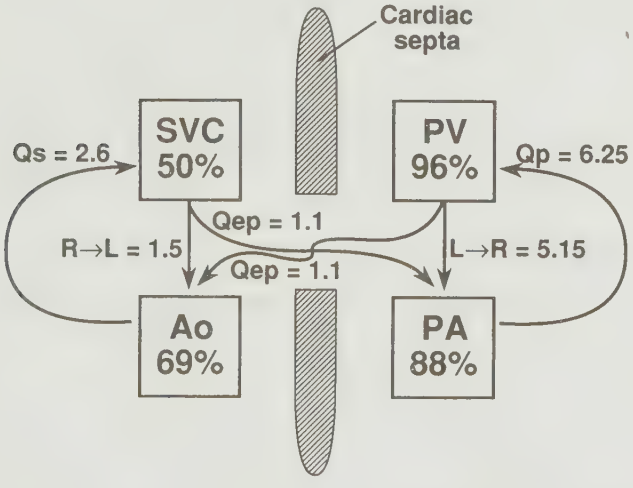


Fig. 54–8. Rearranged "correct" diagram for transposition of the great arteries. Comparison of this figure with Figure 54–7 shows that even though the arrows and boxes are rearranged, the blood flow is unchanged between the two figures. However, this figure better represents a patient with transposition of the great arteries because the aorta arises from the right ventricle and SVC, while the pulmonary artery arises from the left ventricle and the left atrium. Thus, patients with TGA automatically have large right-to-left and left-to-right shunts, respectively.

For this example we will use calculations based on a "normal" person who has a VO_2 of 150 mL O_2/min, a hemoglobin of 15 g/dL, an arterial oxygen saturation of 95%, and arterial Po_2 of 80 mm Hg, a venous saturation of 70%, and a venous Po_2 of 40 mm Hg. Dissolved oxygen in the blood contains 3.26 mL O_2/L at an oxygen tension of 100 mm Hg (or 0.03 ml O_2/mm Hg in 1.0 L of blood). Remember that at an oxygen saturation of 100%, each gram of hemoglobin in a liter of blood will combine with 13.6 mL of O_2; thus, if the hemoglobin is 15 g/dL the O_2 capacity would be 204 mL O_2/L. The hemoglobin of the arterial blood will contain 193.8 mL O_2/L; in the venous blood the hemoglobin will contain 142.8 mL O_2/L. The volume of dissolved oxygen in the arterial and venous blood will be 2.4 and 1.2 mL O_2/L, respectively.

The Qp using only oxygen combined with hemoglobin in this example is

$$Qp = \frac{150}{193.8 - 142.8} = 2.94 \text{ L/min}$$

The Qp using the oxygen content is

$$Qp = \frac{150}{(193.8 + 2.4) - (142.8 + 1.2)} = 2.87 \text{ L/min}$$

An insignificant difference!

The lower the red cell mass and the higher the FiO_2, the greater the percentage of dissolved oxygen in the blood. Whenever there is anemia, there will be less oxygen bound to hemoglobin. Whenever there is a high concentration of inspired oxygen, the amount of dissolved oxygen in the blood increases. However, even in a person with a hemoglobin of 10 g/dL and an arterial oxygen tension of 600 mm Hg, the dissolved oxygen still only accounts for 14% of the oxygen content.

For practical purposes, the dissolved oxygen becomes important only when determining the pulmonary blood flow in patients with left-to-right shunts who are breathing high concentrations of oxygen. For example, let us assume a child has a VO_2 of 150 mL O_2/min with a hemoglobin of 12 g/dL, the O_2 capacity is, therefore, 163.2 mL O_2/L (13.6 × 12 = 163.2). Representative values for such a patient with a large left-to-right shunt breathing 100% oxygen are 1) pulmonary vein oxygen saturation of 100% with an oxygen tension of 500 mm Hg, and 2) pulmonary artery saturation of 95% with a dissolved oxygen tension of 80 mm Hg. The oxygen content in the pulmonary venous blood is 178.2 mL O_2/L, consisting of 163.2 mL bound to hemoglobin and 15 mL of dissolved oxygen. In the pulmonary artery the oxygen content is 157.4 mL O_2/L, consisting of 155 mL bound to hemoglobin and 2.4 mL dissolved in the plasma. In this case the Qp using only the oxygen combined with hemoglobin is

$$Qp = \frac{150}{163.2 - 155.0} = 18.3 \text{ L/min}$$

However, if the oxygen content is used, the Qp is

$$Qp = \frac{150}{178.2 - 157.4} = 7.2 \text{ L/min}$$

A striking difference! As this example demonstrates, the dissolved oxygen must be used whenever calculating Qp in a patient breathing oxygen who has a large left-to-right shunt.

Normal values for oxygenation saturations are shown in Table 54–5. A high cardiac output and a left-to-right shunt are the two most common causes of elevated values in the pulmonary artery. A low cardiac output, low systemic arterial oxygen saturation, and increased oxygen extraction (such as occurs with anemia or high metabolic rates) all cause low saturations in the "right heart." Abnormally high arterial saturations are almost always due to the patient receiving oxygen. Low saturations in the "left heart" are usually due to lung disease, such as atelectasis or pulmonary edema, or to intracardiac right-to-left shunts. Whenever a low arterial oxygen saturation is unexpectedly obtained, one should obtain an arterial blood gas to determine if the patient's hypoxemia is associated with hypoventilation (or acidosis) from causes such as excessive sedation or lung disease. Treatment should be instituted as indicated.

Oxygen saturations are important in determining pulmonary vascular resistance and pulmonary blood flow, especially in patients with left-to-right shunts who have pulmonary hypertension. If the patient has not been in a steady state, for whatever reason (though in young children and babies it is usually due to awakening and crying), the values obtained for oximetric and pressure measurements will vary too much to be meaningful. If exact measurements for calculation of pulmonary resistance are felt to be necessary, we sedate the patient with enough medication to keep the patient asleep for 15 minutes. We first measure pressures and oxygen saturations in room air. We then repeat these measurements while the patient is breathing oxygen, as pulmonary blood flow often increases (and resistance decreases) during oxygen inhalation; additionally, the sedation may cause hypoxemia and hypercarbia.[37] By following the protocol discussed in the Resistance section of this chapter we are usually able to obtain the majority of the hemodynamic data required in children with pulmonary hypertension.

Table 54–5. Normal Oxygen Saturation

Site	*Average*	*Range*
Superior vena cava	74%	67–83%
Inferior vena cava	78%	65–87%
Right atrium	75%	65–87%
Right ventricle	75%	67–84%
Pulmonary artery	75%	67–84%
Left atrium	95%	92–98%
Left ventricle	95%	93–98%
Systemic artery	95%	92–98%

There is a wider variation in the saturations in the inferior vena cava compared to the superior vena cava, and in the right atrium compared to the right ventricle. These differences in oxygen saturation are due to different saturations of the veins which enter the inferior vena cava and right atrium. For example a very high saturation may be obtained in the inferior vena cava if one samples near the entrance of the renal veins; similarly, a very low saturation in the right atrium may be obtained if one samples near the orifice of the coronary sinus. This oxygen saturation data should be considered approximate because of the significant difference in data obtained from various series plus the amount of sedation and anesthesia varies widely throughout the United States and the rest of the world. References 11, 17, 26, and 39.

Pulmonary venous saturations are also extremely variable. Because of this, many cardiologists use the left atrial saturation for the average or mixed pulmonary venous saturation. However, we routinely use the pulmonary vein saturation, realizing that there can be a marked variance in pulmonary vein oxygenation. The lower (most dependent) portion of the lung has the lowest oxygen saturations.[38] Also, the lung has disproportionate flow, with the left upper lobe having a small percentage of the total lung flow, while the right lower lobe has about three times more pulmonary blood flow. In children with a congenital heart lesion, atelectasis is often present (especially in the left lung when the left atrium is enlarged and compresses the bronchus) and will cause desaturation from the corresponding pulmonary vein.

No matter how meticulous one is in obtaining oximetric data, the results will never be entirely correct because of unavoidable inaccuracies in how we are able to obtain blood samples. These inaccuracies include variation in the steady state, physiological shunting, and sampling errors due to the shunts themselves. Fortunately, these inherent errors do not materially affect most hemodynamic data. For accurate hemodynamic information it is preferable to measure the patient's pressure and oxygen saturation while the patient is quiet, not anxious, and free of any medications that might affect pulmonary or systemic blood flow. In children this is almost impossible, as almost all anesthetics and sedatives cause vasodilatation, which usually diminishes the left-to-right shunt (or increases the right-to-left shunt). We routinely use ketamine, which increases systemic resistance and will increase any left-to-right shunt (or diminish a right-to-left shunt). Blood samples and pressures should be obtained before injection of contrast material, although in many complex congenital heart lesions this is not practical, as mentioned earlier.

Most individuals have physiological right-to-left shunts from thebesian and coronary veins entering the left ventricle and left atrium, and from bronchial veins draining into the left atrium or pulmonary vein. Physiological left-to-right shunting occurs whenever the bronchial arteries drain into the pulmonary artery. These volumes are usually small and are never taken into account except for the patient who has a large bronchial arterial collateral blood supply.

There are various congenital cardiovascular anomalies in which it is virtually impossible to calculate the pulmonary or systemic blood flow (or their vascular resistance). In most patients this is because the proportion of blood flow to the body or lungs is not calculable. For example, in a patient with a large left-to-right shunt due to arterial collaterals entering the distal pulmonary vascular bed, it is usually impossible to obtain a blood sample distal to the shunt. On the other hand, in a patient who has a right-to-left shunt through a PDA it is essentially impossible to determine what the proportion of desaturated blood flowing to the descending aorta is compared with the oxygenated blood flowing into the ascending aorta. Similarly, in coarctation of the aorta one cannot determine what the overall average arterial pressure is because the proportion of blood flowing to the upper half of the body compared to the amount flowing to the lower half is unknown.

Double Left-to-Right Shunts

Various formulas are available for calculating left-to-right shunts at two levels (e.g., an ASD and a VSD). The results of such calculations are almost always inaccurate because they as-

sume complete mixing of the blood (which probably never occurs) in each cardiac chamber that has a shunt.

Rather than using the formulas for determining two left-to-right shunts, the easiest way for us to figure out this type of calculation is to determine the Qp, Qs, Qep, and the left-to-right shunt *as if only one shunt were present*. Let us assume that we have a patient (demonstrated in Fig. 54–9) who has an ASD and a VSD with a 70% mixed venous oxygen saturation, a pulmonary artery saturation of 90%, and arterial saturation of 95%. In this patient the VO_2 is 100 mL O_2/min, the O_2 capacity is 163.2 mL O_2/L (therefore, the hemoglobin is 12 g/dL as 163.2 ÷ 13.6 = 12). Thus, Qep and Qs calculate to be 2.45 L/min, Qp 12.25 L/min, and the total left-to-right shunt to be 9.80 L/min.

$$Qs = \frac{100}{(0.95 - 0.70)163.2} = 2.45 \text{ L/min}$$

$$Qep = \frac{100}{(0.95 - 0.70)163.2} = 2.45 \text{ L/min}$$

$$Qp = \frac{100}{(0.95 - 0.90)163.2} = 12.25 \text{ L/min}$$

$$\text{Left-to-right shunt} = 12.25 - 2.45 = 9.80 \text{ L/min}$$

The only problem remaining is deciding which portion of the left-to-right shunt is by way of the ASD and which portion is by way of the VSD. Just looking at the percent saturations in Figure 54–9, one might assume that the atrial and ventricular shunts are equal because the saturation increases 10% in the right atrium and 10% in the right ventricle. However, this is not true because equal volumes of fully saturated blood will increase the mixed venous saturation more in the proximal than in the distal right-sided chamber. In this example, it will require approximately five times more 95% saturated blood to raise the right atrial saturation from 80% to 90% than was needed to raise the mixed venous saturation from 70% to 80%.

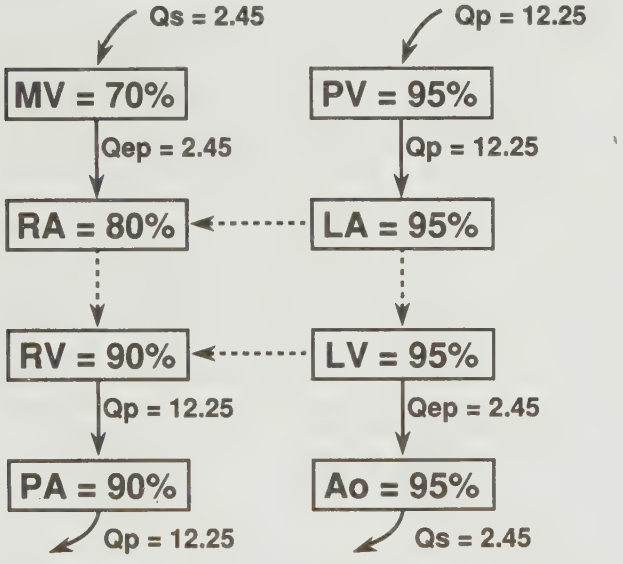


Fig. 54–9. Total intracardiac shunting in a patient with two left-to-right shunts: the location of the boxes in this diagram is somewhat different than in the other recent figures. As discussed in the text, Qp calculates to be 12.25 L/min, and both Qep and Qs calculate to be 2.45 L/min. Thus, the left-to-right shunt is 9.80 L/min. All that remains to do with this diagram is to decide how much of the shunt is at the atrial level and how much is at the ventricular level; these last two shunts (and blood flows) are indicated by dashed lines in this figure because they have not yet been calculated.

Getting back to how calculate a double left-to-right shunt, we have already worked out what the flows are except for what they are inside of the heart. The next step is to assume that the only shunt present is the left-to-right shunt at the atrial level, as shown in Figure 54–10. If this is the case, the right atrial saturation would remain at 80%, but the pulmonary artery saturation would also be 80%. Thus, the Qp, if there was not a VSD, would be 4.08 L/min and the left-to-right atrial shunt would be 1.63 L/min. *Therefore, if the left-to-right shunt at the atrial level is 1.63 L/min when the pulmonary artery saturation is 80%, and the total left-to-right shunt is 9.80 L/min when there is a VSD, then the left-to-right shunt from the VSD has to be 8.17 L/min.*

While we believe that it is easier to "logically" calculate two left-to-right shunts using the method just shown, Figure 54–11 shows a formula for calculating two left-to-right shunts.

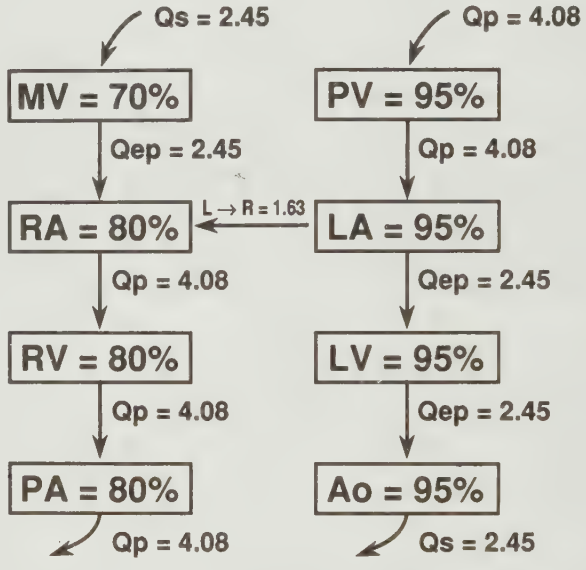


Fig. 54–10. Calculating the first intracardiac shunt in a patient with two left-to-right shunts: assume the same patient as in Figure 54–9, but the VSD closed temporarily; otherwise the shunt at the atrial level remains the same. In this case QP would be 4.08 L/min.

$$Qp = \frac{100}{(0.95 - 0.80)(163.2)} = 4.08$$

Therefore, the left-to-right shunt at the atrial level would be 1.63 L/min (4.08 − 2.45). Suppose the VSD spontaneously opens and all of the intracardiac shunts remain the same except that the right ventricular and pulmonary artery saturation increased to 90%. Since we know from Figure 54–9 that the total left-to-right shunt is 9.80 L/min, then 8.17 L/min must occur at the ventricular level; because, as we just determined, the atrial shunt was 1.63 L/min. This calculation is also described in the text.

$$S = \text{flow} \times \frac{a - b}{c - a}$$

where:

S = left to right shunt into a chamber
flow = blood flowing forward into a chamber
a = oxygen saturation or content in the chamber receiving the shunted blood
b = oxygen saturation or content in the chamber proximal to the shunt
c = pulmonary venous oxygen saturation or content

∴ shunt at ASD in figure 9 would be 1.63 L/min

$$S = 2.45 \times \frac{80\% - 70\%}{95\% - 80\%} = 1.63$$

and ∴ shunt at VSD would be 8.16 L/min as flow = 1.63 +2.45, a = 90%, b = 80%, c = 95%

$$S = 4.08 \times \frac{90\% - 80\%}{95\% - 90\%} = 8.16$$

Fig. 54–11. Formula for calculating two left-to-right shunts: see text for explanation and compare values with Figures 54–9 and 54–10.

OXYGEN CONSUMPTION

Classically, cardiac output (CO) is measured by the Fick principle. The formula is

$$CO = \frac{VO_2}{AVO_2 \text{ difference}}$$

The cardiac output is the quantity of blood delivered to the systemic circulation over a period of time and is usually expressed in liters of blood flowing each minute (L/min). The *arterial venous oxygen (AVO$_2$) difference* is the amount of oxygen extracted from the circulation as the blood flows through a vascular bed and is usually expressed in volumes percent (mL O$_2$/100 mL). The *oxygen consumption (VO$_2$)* is the amount of oxygen taken up by the tissues and is usually expressed in mL of oxygen consumed by the body each minute (mL O$_2$/min). In the catheterization laboratory, VO$_2$ is measured as the amount of oxygen breathed in by the lungs; this is not always the same as the oxygen consumed by the tissues.

In the previous section on oximetry there were multiple examples of calculating the CO, except there it was abbreviated as Qs. Also, there were many examples of how to determine the AVO$_2$ difference, which is the difference in oxygen content across a vascular bed. From all the examples in the oximetry section, it is apparent that the Fick principle also applies to the flow across the pulmonary vascular bed, where

$$Qp = \frac{VO_2}{AVO_2 \text{ difference across the lungs}}$$

This section will concentrate on the most difficult part of measuring the CO (or the Qs or the Qp), which is how to determine the VO$_2$. But first we will use a simple example to demonstrate the Fick principle. The reader will recognize that this example is identical to the examples in the previous section, but that the equation is expressed slightly differently. A patient who is known to have a VO$_2$ of 240 mL O$_2$/min and an AVO$_2$ of 4 vol%, will have a cardiac output of 6 L/min, as shown by the following calculation:

1. Four vol% is the AVO$_2$ difference in a person with a hemoglobin of 15 g/dL, 95% saturated arterial blood, and 75% saturated venous blood.
2. The VO$_2$ was 240 mL O$_2$/min.
3. The AVO$_2$ difference is 4 vol%, which is 4 mL O$_2$/dL or 40 mL O$_2$/L.
4. Therefore, the cardiac output is

$$\frac{VO_2}{AVO_2 \text{ difference}} = \frac{240 \text{ mL } O_2/\text{min}}{40 \text{ mL } O_2\text{L}} = 6 \text{ L/min}$$

This is exactly what Adolph Fick postulated in 1870.[40] He stated that the difference of oxygen in the arterial and venous blood had to be supplied by the lungs, and that from this fact one could calculate the cardiac output. Fick never did the experiments himself, but, based on animal data, he calculated that the human VO$_2$ would be 5 mL O$_2$/sec, and the amount of blood ejected during each systole would be 77 mL. His estimates were close to present-day normal values: a VO$_2$ of 5 mL O$_2$/sec is 300 mL O$_2$/min; and the cardiac output calculated to be 5.39 L/min, as he assumed the heart rate to be 70 beats per minute (77 mL × 70 BPM = 5390 mL/min).

The normal oxygen consumption for children 5 to 15 years old is about 110 to 160 mL O$_2$/min (per M^2), and for 0 to 5 years old it ranges from 160 to 200 mL O$_2$/min (per M^2).[28,41–43] The normal cardiac output for most children is about 4.0 to 5.0 L/min (per M^2), with slightly higher values for newborns.[39,41,42]

The classic way of measuring VO$_2$ is to collect all the expired air in a Douglas bag over a 3- to 5-minute period. The volume of expired air (VE) is measured with a Tissot spirometer and the amount of oxygen is measured with an oxygen analyzer (sometimes the amount of CO$_2$ is also measured). The amount of oxygen taken up by the lungs and consumed by the body is calculated by multiplying the volume of expired air collected in the bag by the fractional difference between inspired and expired oxygen. Since dry room air has 20.93% oxygen, all one has to know to calculate VO$_2$ is the volume of air in the bag and the concentration of oxygen in the expired air. For example, if 3750 mL of air was collected over a 5-minute period and the fraction of oxygen in the expired air was 0.1793, then the VO$_2$ would be 22.5 mL O$_2$/min. FiO$_2$ and FeO$_2$ stand for the fraction of inspired and expired oxygen, and that VE is measured in volume per minute. Thus, the formula for VO$_2$ is

$$VO_2 = VE(FiO_2 - FeO_2)$$

$$VO_2 = (3750 \div 5)(0.2093 - 0.1793) = 22.5 \text{ mL } O_2/\text{min}$$

For exact measurement of the amount of oxygen consumed, the inspiratory volume of air (VI) should be used, and the "true" formula for measuring oxygen consumption is VO$_2$ = [(VI) × (FiO$_2$)] − [(VE) × (FeO$_2$)]. Which is, of course, correct, as VO$_2$ has to be the difference between the volume of O$_2$ in inspired air and the volume of O$_2$ in the expired air. For practical purposes VO$_2$ is usually determined without measuring VI, as the VE is usually equal to or only slightly less than the VI.

An additional error not taken into account with the first formula for VO$_2$ is that the amount of oxygen breathed in is often different from the amount of carbon dioxide breathed out (CO$_2$). Originally

this was known as the respiratory quotient, but the term respiratory exchange ratio (RER) is now used. The formula is

$$RER = \frac{VCO_2}{VO_2}$$

While metabolizing carbohydrates, the RER is 1.0. While metabolizing fat, the RER is about 0.70. The RER when metabolizing protein is around 0.82. The explanation for this is that during metabolism fats and proteins require proportionately more oxygen than do carbohydrates.[44] Carbohydrates are made up of equal amounts of carbon and oxygen. Thus, in the breakdown of glucose the RER will be 1.0, because 6 moles of O_2 form 6 moles of CO_2 and water, as shown in the following formula:

$$C_6H_{12}O_6 + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O$$

However, when palmitin, the triglyceride of palmitic acid, is metabolized 145 moles of O_2 are consumed but only 102 moles of CO_2 and 98 moles of water are produced. Thus, the RER is 102/145 = 0.70.

$$2C_{51}H_{98}O_6 + 145\ O_2 \rightarrow 102\ CO_2 + 98\ H_2O$$

Depending on how VO_2 is measured, if VE is assumed to equal VI (RER = 1.0), whenever the RER is 0.8, VO_2 will be underestimated by about 4%. If the RER is 0.9, the VO_2 will be underestimated by about 2%. For practical purposes if one assumes VE = VI, the RER will never be so low that one would underestimate VO_2 by more than 6 to 7%. An example of how VO_2 is underestimated is shown in the next paragraph.

Let us assume that we have a patient who inhaled 5000 mL of air during a minute. From this 5000 mL of air he extracts 250 mL of O_2 and exhales 200 mL of CO_2. By definition his RER would be 0.8. Since the volume of nitrogen (and the other inert gases) does not exchange in the lungs, the VE would be 4950 mL instead of 5000 mL because 50 mL of O_2 was not replaced by CO_2. Though VI cannot be measured, it can be calculated from the fact that the volume of inspired air multiplied by the fraction of the sum of each of its component gases is equal to the volume of expired air multiplied by the fraction of the sum each of its component gases. The formula for this is

$$(VI \times FiN_2) + (VI \times FiO_2) + (VI \times FiCO_2)$$

$$= (VE \times FeN_2) + (VE \times FeO_2) + (VE \times FeCO_2)$$

Using the above formula we will now calculate the error in the example in the above paragraph if we assume the formula for $VO_2 = VE(FiO_2 - FeO_2)$ if the RER is 0.8; this is shown in Table 54–6. The fractions of nitrogen, oxygen, and CO_2 in dry inspired air are always 0.7904, 0.2093, and 0.0003 respectively (line 1). In the 5000 mL of inspired air, the volume of the three gases would be distributed as shown in line 2. Line 3 shows the amount of O_2 inhaled and CO_2 exhaled when the VO_2 is 250 ml and the RER is 0.8. Line 4 shows the volume of each of these gases in the expired air. The expired air has the same amount of nitrogen, but has 250 mL less of O_2 and 200 mL more of CO_2. The fraction of each gas is shown in line 5. If the formula $VO_2 = VE(FiO_2 - FeO_2)$ is used to calculate VO_2, then we obtain a value of 240 mL/min as shown in line 6. This is 10 mL less than the true value of VO_2 of 250 mL as shown in line 7. Thus, with this RER of 0.8, the VO_2 will be underestimated by 4% with this formula.

The reason for this error is that by measuring VE one always understimates VI whenever the RER is less than 1.0. The example in Table 54–6 did not consume 240 mL O_2 from 4950 mL of air, he actually consumed 250 mL O_2 from 5000 mL of inspired air. In this example if the extra 50 mL of CO_2 had been added to the VE (i.e., an RER of 1.0), then the value for the VO_2 would have been correct as $VO_2 = VE(FiO_2 - FeO_2) = 5000\ (0.2093 - 0.1593) = 250$ mL O_2/min. Similarly, if the correct formula for measuring oxygen consumption had been used, i.e., $VO_2 = (VI \times FiO_2) - (VE \times FeO_2) = (5000 \times 0.2093) - (4950 \times 0.1609) = 250$ mL O_2/min, then VO_2 would not have been underestimated.

Formulas are available for correcting the VO_2 when the RER is less than 1.0. These are based on the assumption that nitrogen does not exchange in the lungs and therefore $(VI) \times (FiN_2) = (VE) \times (FeN_2)$. Nitrogen cannot be measured in most laboratories, but VE, FeO_2, and $FeCO_2$ are relatively easy to measure. Thus, the various formulas used for obtaining an accurate value for VO_2 factor out nitrogen and substitute oxygen and carbon dioxide for nitrogen. This is demonstrated in Table 54–7, which shows how one of these formulas is derived. The formula on line 5 of the table will correct the VO_2 whenever VE is less than VI. Since the error for neglecting to measure CO_2 and correcting for RER is small, most laboratories use the simplified formula for calculating VO_2; namely $VO_2 = VE(FiO_2 - FeO_2)$. VO_2 by this formula is usually within 6 to 7% of the actual VO_2, as discussed earlier.

Fortunately, VO_2 no longer needs to be measured by the cumbersome and complex Douglas bag method. Presently VO_2 is almost always measured by the polarographic method.[45,46] In this method, a known amount of air is passed through a hood placed over the patient's head and the concentration of oxygen is determined at the outlet end of the hood. Since the volume of the air blowing through the hood is known, plus the initial concentration of oxygen is known to be 20.93%, the concentration of oxygen

Table 54–6. Error in VO_2 When RER is 0.8

	N_2	O_2	CO_2	*Total*
1. Fraction of VI	0.7904	0.2093	0.0003	1.000
2. VI Volumes	3952 mL	1046.5 mL	1.5 mL	5000 mL
3. O_2/CO_2 exchange	N/A	−250 mL	+200 mL	−50 mL
4. VE volumes	3952 mL	796.5 mL	201.5 mL	4950 mL
5. Fraction of VE	0.7984	0.1609	0.0407	1.000
6. Calculated $VO_2 = VE\ (FiO_2 - FeO_2) = 4950\ (0.2093 - 0.1609) = 239.6$ mL O_2/min				
7. "True" $VO_2 = (VI \times FiO_2) - (VE \times FeO_2) = (5000 \times 0.2093) - (4950 \times 0.1609) = 250$ mL O_2/min				

Table 54–7. Derivation of Formula for Measuring VO_2 When RER <1.0

1. Since there is no exchange of nitrogen in the lungs:

$$VI = (VE) \times \left(\frac{FeN_2}{FiN_2}\right)$$

2. A. FiN_2 is always 0.7904,
   B. FeN_2 is the fraction of gas which remains after the CO_2 and O_2 fractions are subtracted, which is $[1 - (FeO_2 + FeCO_2)]$
   C. Therefore, the formula on the line 1 is the same as

$$VI = \frac{VE\,[1 - (FeO_2 + FeCO_2)]}{0.7904}$$

3. The formula for VO_2 is: $VO_2 = [(VI)\,(FiO_2)] - [(VE)\,(FeO_2)]$
4. By substituting the formula on line 2C for VI, the formula on line 3 becomes:

$$VO_2 = \left[\left[\frac{VE\,(1 - (FeO_2 + FeCO_2)}{0.7904}\right] \times [FiO_2]\right] - \left[(VE) \times (FeO_2)\right]$$

5. A. FiO_2 is always 0.2093
   B. VE can be factored out from the formula in line 4
   C. and with rearranging, the formula on line 4 becomes:

$$VO_2 = VE\left[\left(\frac{0.2093}{0.7904} \times (1 - [FeO_2 + FeCO_2])\right) - FeO_2\right]$$

6. Using the values present in Table 54–6 demonstrates that the above formula gives the correct VO_2.

$$VO_2 = 4950\left[\left(0.2648\,[1 - (0.1609 + 0.0407)]\right) - [0.1609]\right] = 250 \text{ ml } O_2/\text{min}$$

at the outlet end can be used to calculate how much oxygen has been taken up by the patient. The readings for VO_2 are automatically displayed in a very short time after the child is placed under the hood. Older instruments used a RER of 1.0 for calculation of VO_2; more modern models use a RER of 0.85, which is closer to the actual RER in most patients.

Many times, it is not practical to measure the oxygen consumption. In this case one can use the tables of LaFarge and Miettinen to estimate VO_2.[43] These tables are based on age, sex, and heart rate. They assume that the patient has been premedicated with the standard "Toronto mixture" of meperidine, chlorpromazine, and promethazine, with some children receiving chloral hydrate as additional sedation. Because these tables are frequently used they are reproduced in Table 54–8.

All of the means of measuring VO_2 are subject to error, even if the RER of the patient is 1.0. Direct collection of air may result in leakage of air from the seal or tubing between the patient and the bag. The polarographic method may have too high or low air flow for accurate measurements. Oxygen consumption tables are based on calculations of average values for many children and may not pertain to an individual patient especially when the catheterization is done at a different institution using different techniques. The amount of oxygen that one measures is the amount of oxygen inhaled; if the patient either hyper- or hypoventilates, the oxygen inhaled will not equal the amount of oxygen actually delivered to the pulmonary and systemic capillaries. All measurements of VO_2 assume that the patient is in a steady state and that the oxygen consumption and cardiac output are constant. If they are not, the amount of oxygen inserted into the pulmonary vascular bed will not necessarily equal the oxygen consumed by the tissues.

Also, we are actually measuring the aortic oxygen content rather than the pulmonary venous oxygen content. Thus, any of the bronchial or thebesian venous blood that drains into the pulmonary veins, left atrium, or left ventricle will cause the aortic saturation to be less than the true sum of the pulmonary venous blood saturation, though in most cases this is estimated to be less than 2 to 5 mL O_2/L. Similarly, bronchial collateral arterial supply to the pulmonary vascular bed, which is often increased in children with cyanotic forms of congenital heart lesions, will result in an unmeasurable left-to-right shunt as the sample of blood taken from the pulmonary artery will almost always be proximal to where these arteries enter the pulmonary vascular bed. In this case, if the left-to-right shunt is large, the AVO_2 difference across the lungs will be underestimated and it will be impossible to calculate Qp or the cardiac output (Qs).

Finally, as with all tests, there is an inherent error in determining both the VO_2 and the AVO_2 difference; the total error in determination of the cardiac output by the Fick oxygen method has been estimated to be about 10%.[47]

When expired air is collected, its volume is measured at the *ambient* (room) *temperature* and barometric *pressure,* plus it is fully *saturated* with water vapor—abbreviated as VE_{ATPS}. Because oxygen volumes are given at standard temperature (273 degrees Kelvin or 0 degree Celsius) and pressure (760 mm Hg) which is dry (all water vapor removed), it is customary to convert VE_{ATPS} to *standard temperature* and *pressure, dry*—abbreviated as VE_{STPD}. This conversion of VE_{STPD} from VE_{ATPS} is done using Boyle's law (the volume of a gas varies inversely with its pressure) and Charles' law (the volume of a gas varies directly with its temperature). In converting VE_{ATPS} to VE_{STPD} it is necessary to add the room temperature (in degrees C) to the Kelvin temperature (273 degrees), and to subtract the partial pressure of water vapor from the barometric pressure. There are tables that show what the water vapor is at different temperatures. However, at the usual room temperature, of 20 to 25°C the partial pressure of water vapor is 18 to 24 mm Hg.

Table 54–9 shows a typical calculation of converting VE_{ATPS} to VE_{STPD}: VE_{ATPS} was 5000 mL. The room temperature was 22°C (at 22°C the vapor pressure of water is 19.8 mm Hg) and the barometric pressure was 759 mm Hg. Note that in this example in Table 54–9, the VE_{STPD} was exactly 90% of the VE_{ATPS}. At most room temperatures at sea level, the conversion factor from VE_{ATPS} to VE_{STPD} will always be approximately 0.9.

RESISTANCE

The calculation of vascular resistance is analogous to measuring electrical resistance by Ohm's law. The formula for electrical resistance is R = E/I which is the drop in voltage across a wire divided by the amperes flowing through the electrical wire. The formula for hydraulic or vascular resistance is R = P/Q which is

Table 54–8. Oxygen Consumption Per Body Surface Area in (mL/min)/M² by Sex, Age, and Heart Rate

Age	*Heart Rate (beats per minute)*												
	50	*60*	*70*	*80*	*90*	*100*	*110*	*120*	*130*	*140*	*150*	*160*	*170*
Male patients													
3				155	159	163	167	171	175	178	182	186	190
4			149	152	156	160	163	168	171	175	179	182	186
6		141	144	148	151	155	159	162	167	171	174	178	181
8		136	141	145	148	152	156	159	163	167	171	175	178
10	130	134	139	142	146	149	153	157	160	165	169	172	176
12	128	132	136	140	144	147	151	155	158	162	167	170	174
14	127	130	134	137	142	146	149	153	157	160	165	169	172
16	125	129	132	136	141	144	148	152	155	159	162	167	
18	124	127	131	135	139	143	147	150	154	157	161	166	
20	123	126	130	134	137	142	145	149	153	156	160	165	
25	120	124	127	131	135	139	143	147	150	154	157		
30	118	122	125	129	133	136	141	145	148	152	155		
35	116	120	124	127	131	135	139	143	147	150			
40	115	119	122	126	130	133	137	141	145	149			
Female patients													
3				150	153	157	161	165	169	172	176	180	183
4			141	145	149	152	156	159	163	168	171	175	179
6		130	134	137	142	146	149	153	156	160	165	168	172
8		125	129	133	136	141	144	148	152	155	159	163	167
10	118	122	125	129	133	136	141	144	148	152	155	159	163
12	115	119	122	126	130	133	137	141	145	149	152	156	160
14	112	116	120	123	127	131	134	133	143	146	150	153	157
16	109	114	118	121	125	128	132	136	140	144	148	151	
18	107	111	116	119	123	127	130	134	137	142	146	149	
20	106	109	114	118	121	125	128	132	136	140	144	148	
25	102	106	109	114	118	121	125	128	132	136	140		
30	99	103	106	110	115	118	122	125	129	133	136		
35	97	100	104	107	111	116	119	123	127	130			
50	94	98	102	105	109	112	117	121	124	128			

(Reprinted with the kind permission of LaFarge, C.G., and Miettinen, O.S.: The estimation of oxygen consumption. Cardiovasc. Res., *4*:23–30, 1970.)

Table 54–9. Conversion of a Volume Measured at Ambient Temperature and Barometric Pressure Saturated with Water Vapor to Standard Temperature and Pressure Without Water Pressure

1. According to Charles' and Boyle's laws:

$$\frac{PV_{STPD}}{T} = \frac{P'V'_{ATPS}}{T'}$$

2. which is

$$\frac{760 \times VE_{STPD}}{273} = \frac{(P_B - P_{H2O}) \times (VE_{ATPS})}{273 + °C}$$

3. A. Assume that VE was 5000 mL, room temperature 22°C (which gives a partial pressure of water of 19.8 mm Hg), and that the barometric pressure was 759 mm Hg.

   B. Incorporating these values and rearranging the formula on line 2:

$$VE_{STPD} = \frac{(759 - 19.8)\,(5000)\,(273)}{(760)\,(273 + 22)} = 4500 \text{ mL}$$

the drop in pressure across a vascular bed divided by the volume of blood flowing through the vessels.

The calculation for resistance for blood flow is based on Poiseuille's law which states that:

$$R = \frac{P_{in} - P_{out}}{Q}$$

Q is the flow, P_{in} is the mean inflow pressure, P_{out} is the mean outflow pressure, and R is the resistance.

Even though Poiseuille was interested in blood flow, his law was based upon the flow of simple fluids through rigid, cylindrical glass tubes that were constant in shape. It is obvious that resistance must also vary depending upon the size of the tubes and the viscosity of the fluid going through those tubes. The formula for Poiseuille's law is

$$R = \frac{8\,\eta l}{\pi\, r^4}$$

Where r^4 stands for the radius to the fourth power, η for the viscosity of the fluid, l for the length of the vessels, and π for pi.

To use Poiseuille's law for vascular resistance assumes that there is

1. Constant blood viscosity
2. Constant radius and length
3. That the pressure and flow is nonpulsatile
4. That the amount of fluid entering is equal to the amount leaving

None of this is true. Blood is not a uniform homogenous fluid. Blood vessels are elastic and change in size. Blood pressure and flow are obviously pulsatile. Pulmonary vascular resistance increases in an exponential fashion as polycythemia develops, especially at hematocrit values greater than 54%.[48] Furthermore, blood flow is not linearly proportional to the pressure; blood vessels have a "critical closing pressure";[49] and the higher the outflow pressure is, the less the total resistance is.[50] Despite these inaccuracies in measuring vascular resistance, the concept of resistance as opposition to blood flow is firmly established and is used clinically in pediatric cardiology.

Resistance is mainly important in pediatrics when a child has pulmonary hypertension. By rearranging the formula for resistance so that P = QR, it can be seen that increased pressure in the pulmonary artery, which is pulmonary hypertension, can be due to either increased flow or resistance, (assuming that outflow pressure is not elevated such as from mitral stenosis). If there is pulmonary hypertension and the pulmonary blood flow is increased, resistance ordinarily will be normal or only mildly increased, as occurs with a VSD with massive left-to-right shunting. Similarly, if resistance is markedly elevated, as occurs with Eisenmenger's syndrome, then pulmonary blood flow will be relatively minimal.

Review of Poiseuille's law demonstrates that the main factor that determines resistance is the radius. Thus, a radius that is half the size of another blood vessel will have 16 times greater resistance. As an example of this, if all of the blood vessels in the lungs that normally have a 40-micron radius develop narrowing of every one of these blood vessels to 20 microns, then the resistance will become 16 times greater (20^4 is one sixteenth of 40^4).

All patients with a large VSD and no other heart lesion always have pulmonary hypertension as the systolic pressures in the right ventricle, left ventricle, pulmonary artery, and aorta are always equal, because there is no restriction of pressure between the two ventricles. As just mentioned, if pulmonary vascular resistance is low, then pulmonary blood flow will be high in a child with a large VSD; vice versa, if flow is high, resistance is low. *The resistance of the pulmonary vascular bed is directly proportional to the narrowing of the small pulmonary blood vessels.*

Children with an abnormally elevated pulmonary vascular resistance have significant microscopic changes with narrowing of these blood vessels, as described by Heath and Edwards.[51] In these patients surgically closing a VSD does not decrease their pulmonary hypertension. This was recognized early in the history of pediatric cardiac surgery when patients with elevated pulmonary artery pressure had a much higher mortality from surgery and frequently did not have lowering of their pressure following surgery[52,53]: thus, the term "irreversible pulmonary hypertension."

A patient with a VSD who has pulmonary hypertension and has five times the normal amount of pulmonary blood flow obviously cannot have markedly narrowed pulmonary blood vessels. In this case, if the VSD is closed the pulmonary pressure will return to normal. But what about a patient with pulmonary hypertension with a Qp/Qs of 2.0/1? It is in these children with moderately increased flow and pulmonary hypertension in whom calculation of resistance becomes valuable.

Table 54–10 contains formulae for calculating resistance. In calculating resistance it is necessary to have a pressure drop across the vascular bed as shown in Figure 54–12. Previously, many had used the term total pulmonary resistance (TPR) for resistance, and state that this is the pressure the right ventricle faces. However, TPR is a meaningless term because it does not take into account the pressure drop across the vascular bed. For example, if the inflow pressure is 100 mm Hg but the outflow pressure is also 100 mm Hg, then there can be no flow. "TPR" is essentially never used now, because PCW pressure or left atrial pressure is almost always measured during cardiac catheterizations, though this was not necessarily so 25 years ago. Also, in the earlier studies where TPR was used for calculating resistance, left atrial pressure was fortunately usually normal so that whenever there was any increase in TPR it was usually due to narrowing of the pulmonary vascular bed.

There are differing viewpoints as to which is the preferable way to measure pulmonary resistance. Some prefer to use the actual pulmonary vascular resistance (Rp) because this measures the overall reactivity of the pulmonary blood vessels and sometimes this may be independent of any changes in the hemodynamic status of the systemic vascular bed. However, whenever there is a left-to-right shunt, the pulmonary and systemic circulations are interrelated and Rp can never be entirely independent of systemic vascular resistance (Rs). Also, measuring pulmonary resistance requires measuring pulmonary blood flow which may not be accurate, especially in patients who have left-to-right shunts with streamlining of blood into the pulmonary artery.

Calculating Rp/Rs does not require measuring pulmonary or systemic blood flow. Thus, the error in determining VO_2 is eliminated and the error in determining pulmonary AVO_2 difference is reduced. However, changes in the systemic vascular resistance

Table 54–10. Formulae for Vascular Resistance

$$Rp = \frac{\overline{PA}p - \overline{PV}p}{Qp}$$

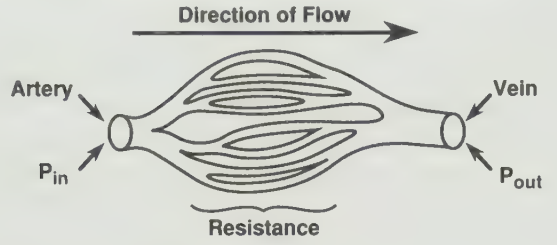
$$Rs = \frac{\overline{AO}p - \overline{RA}p}{Qs}$$

$$\frac{Rp}{Rs} = \frac{\overline{PA}p - \overline{PV}p \times Qs}{AOp - RAp \times Qp}$$

$$TPR = \frac{\overline{PA}p}{Qp}$$

$$TSR = \frac{\overline{AO}p}{Qs}$$

Abbreviations: $\overline{PA}p$, $\overline{PV}p$, $\overline{AO}p$, and $\overline{RA}p$ are the mean pressures of the pulmonary artery, pulmonary vein, aorta, and right atrium. TSR and TPR are the total systemic and pulmonary resistance. Qp and Qs are pulmonary and systemic blood flows. Mean pulmonary capillary wedge pressure or mean left atrial pressure may be substituted for $\overline{PV}p$, any mean systemic arterial pressure may be substituted for $\overline{AO}p$, and mean superior vena cava pressure may be substituted for $\overline{RA}p$. All of these substitutions assume that there is no obstruction to blood flow such as superior vena cava obstruction from a Mustard operation. Rp and Rs are pulmonary and systemic vascular resistances.



Formula:

$$R = \frac{P_{in} - P_{out}}{Q}$$

where:

R = resistance: units = $mmHg \cdot L^{-1} \cdot min$
Q = flow: units = L/min
P_{in}, P_{out} = arterial & venous mean pressure, respectively: units = mmHg

Example of calculation on pulmonary vascular resistance where pulmonary arterial mean pressure is 20 mmHg, pulmonary venous pressure is 5 mmHg and pulmonary blood flow is 5 L/min:

$$R = \frac{20 - 5 \text{ mmHg}}{5 \text{ L/min}} = 3 \text{ mmHg} \cdot L^{-1} \cdot min$$

Fig. 54–12. Resistance of a vascular bed: vascular resistance occurs primarily at the small arteries, arterioles, capillaries, venules, and small veins. Also, as can be deduced from this figure, if the arterial pressure is the same as the venous pressure there can be no flow, which is another way of emphasizing why both arterial and venous pressure must be known in order to calculate vascular resistance.

Table 54–11. Some Factors That May Change Pulmonary Vascular Resistance

1. Changes in pulmonary venous pressure
2. Changes in pulmonary blood flow
3. Changes in pulmonary blood volume
4. Changes in alveolar pressures
5. Changes in intrathoracic pressure
6. Pulmonary edema
7. Changes in size of pulmonary vascular bed
8. Red blood cell concentration
9. Platelet count
10. Blood viscosity
11. Autonomic nervous system tone
12. Intravascular chemoreceptors
13. Intravascular mechanoreceptors
14. Changes in neuroregulation of ventilation
15. Changes in oxygen saturation
16. Changes in ventilation
17. Changes in acid base balance
18. Catecholamines, endogenous
19. Catecholamines, exogenous
20. Acetylcholine
21. Tolazoline
22. Serotonin
23. Histamine
24. Prostaglandins

may result in an abnormally high or low Rp/Rs ratio independent of any changes in the pulmonary vascularity. Despite this potential drawback, some prefer to use the resistance ratio (Rp/Rs), as factors which may be affecting both vascular beds such as cardiac output, blood viscosity, cardiovascular active drugs, degree of sedation, hormonal and neurological factors, and metabolic status will tend to equally affect the systemic and pulmonary vascular bed and will usually "cancel each other out." Table 54–11 lists many factors which can cause changes in the pulmonary vascular resistance.[54]

In patients who have pulmonary hypertension with an elevated pulmonary vascular resistance one should make sure that there are not extrinsic factors causing the hypertension. Such extrinsic factors almost always cause an elevated resistance because they cause vasoconstriction of the smooth muscle in the walls of the small pulmonary blood vessels, which results in a decrease in the effective radius of the pulmonary vascular bed. In practicality, the most common cause of an elevated pulmonary resistance during cardiac catheterization of children is due to sedation, with hypoxemia and hypercarbia causing pulmonary vasoconstriction. The administration of oxygen besides being a direct pulmonary vasodilator also will eliminate any hypoxemia which may be present on the basis of hypoventilation.

We believe that oxygen often is the only agent that is needed to determine whether or not an elevated pulmonary vascular resistance is due to pulmonary vasoconstriction. If the pulmonary resistance diminishes significantly using oxygen as outlined in the protocol in Table 54–12, then there probably is a significant amount of pulmonary vasoconstriction and the pulmonary hypertension in this case may be "reversible." Some authors believe that additional agents such as tolazoline should be used whenever there is an elevated pulmonary resistance.

Brammel and Vogel in discussing the Eisenmenger's syndrome believe that all patients with a pulmonary vascular resistance of equal or greater than 600·dynes·sec·cm^{-5}·M^2 should receive tolazoline, and if the resistance decreases to less than 450·dynes·sec·cm^{-5}·M^2, then there is a chance that the pulmonary vascular resistance is reversible.[55]

Normal systemic vascular resistance is 9–12 mm Hg·min·L^{-1}·M^2 in infants and 13 to 18 mm Hg·min·L^{-1}·M^2 in older children. Normal pulmonary vascular resistance is usually less than 2 mm Hg·min·L^{-1}·M^2.[17] Using representative values for pressures from Table 54–2 and the formula from Table 54–10, the normal Rp/Rs is less than 0.1/1. Note that in this calculation Qp/Qs is 1.0/1 as normal individuals have equal pulmonary and systemic blood flows. Thus:

$$\frac{Rp}{Rs} = \frac{12 - 7 \text{ mm Hg}}{80 - 3 \text{ mm Hg}} \times \frac{1}{1.0} = \frac{5}{77} = <0.1/1$$

The units most commonly used to measure pulmonary and systemic resistance are mm Hg·min·L^{-1} as one measures the pressure drop in mm Hg, and measures the cardiac output in L/min. These are also known as hybrid resistance units or HBU, and are also called Wood units,[56] the latter named after the famous cardiologist Paul Wood. In determining resistance there seems to be some confusion as to whether the units should be "divided or multiplied" when the units in the denominator are placed in the same line as the numerator. Often resistance units will be expressed as mm Hg/L/min, or indexed as mm Hg/L/min/M^2, which is dis-

Table 54–12. Protocol for Calculating Pulmonary Resistance in Children With Left-to-Right Shunts and Pulmonary Hypertension

A. Place catheters in pulmonary artery and systemic artery.
B. Measure oxygen consumption while breathing room air.
C. While breathing room air:
   1. Obtain pulmonary artery O_2 saturation and pressures.
   2. Measure simultaneous systemic arterial O_2 saturation, pressure and blood gases.
   3. Withdraw catheter to SVC.
   4. Obtain SVC O_2 saturation and pressure.
   5. Insert catheter into left atrium.*
   6. Obtain left atrial O_2 saturation and pressure.
D. Have patient breathe oxygen (FiO_2 >0.5) by face mask for 5 to 10 minutes, and then while the patient is still breathing oxygen, obtain the following:
   1. Insert catheter back into pulmonary artery.
   2. Obtain pulmonary artery O_2 saturation, pressure and blood gases.
   3. Obtain simultaneous systemic arterial O_2 saturation, pressure and blood gases.
   4. Withdraw catheter to SVC.
   5. Obtain SVC O_2 saturation and pressure.
   6. Insert catheter into left atrium.*
   7. Obtain left atrial O_2 saturation, pressure and blood gases.

*If unable to enter the left atrium, pulmonary capillary wedge pressures may be obtained in the pulmonary artery and assumed to be equal to the left atrial pressures. In this case, assume that the left atrial saturation is equal to the systemic arterial saturation. Later in the catheterization, confirm that the left atrial saturation is equivalent to systemic arterial saturation by injecting green dye into the IVC and SVC with sampling in the systemic artery to confirm that no right to left shunt is present.

We withdraw the catheter to the SVC rather than the right atrium because we have found the SVC saturation to correlate better with the pulmonary artery saturation in normal individuals. If the left atrium is entered and the left atrial saturation or arterial blood gases are significantly higher than the systemic arterial saturation or blood gas then one must assume that some right to left shunting is present.

After the above data has been obtained, calculate pulmonary and systemic resistances both while breathing room air and while breathing oxygen. In the calculations made while breathing oxygen, one must include the dissolved oxygen as part of the oxygen content.

cussed at the end of this section. The correct units of measurement are

$$R = \frac{P}{Q} = \frac{\text{mm Hg}}{\text{L/min}} = \frac{\text{mm Hg·min}}{\text{L}} = \text{mm Hg·min·L}^{-1}$$

By multiplying by 80, hybrid units can be converted to the cgs system where the units are dynes·sec·cm^{-5}. These are also known as the absolute resistance units or ARU.

The important question is: *Is the resistance too elevated to consider doing cardiac surgery?* In general, an Rp of less than 5 units·M^2 and a resistance ratio of less than 0.4/1 often means that the pulmonary hypertension may be due to increased pulmonary blood flow and it is possible that the pulmonary pressure will diminish with repair of the lesion. An Rp of greater than 10 units·M^2 and Rp/Rs of greater than 0.7/1 usually means that surgery will have a significantly increased mortality and/or that the pulmonary hypertension will not resolve following surgery.

The trouble with applying these values for determining whether to perform surgery is that the studies on which these numbers are based were performed at multiple centers; the studies were done in different lesions, the sedation and duration of catheterization were different from institution to institution, etc. Additionally, some series used surgical results, other used postoperative catheterization results, others used lung biopsy results, and other used autopsy results. Therefore, it is difficult to state, from a resistance standpoint, exactly when the pulmonary resistance is too elevated to perform cardiac surgery. Table 54–13 summarizes the results of some of these reports.

One of the areas of confusion we have seen in measuring resistance and indexing it to body surface area (BSA) is that there is confusion as to whether resistance is divided or multiplied by the BSA. It is *multiplied* by the BSA, as was first pointed out to us by Dr. Dwight McGoon.[63] The formula for pulmonary vascular resistance is:

$$\frac{\overline{PAp} - \overline{PVp}}{Qp}$$

To index the resistance value according to body size, the initial instinct seems to be to divide the units of resistance by the body surface area (BSA). However, simple logic exposes the fallacy of that approach. Let us suppose that a 1-year-old baby and an adult each has a large VSD. The pulmonary artery minus the pulmonary venous pressure could be quite similar in the two, but pulmonary blood flow would obviously be several times higher in the adult because of the much larger lungs in the adult. Thus, the value for calculated pulmonary resistance prior to "indexing" for BSA would be much lower in the adult than the child.

The purpose for indexing is to allow more meaningful comparisons between patients of widely differing sizes. However, to divide their resistance levels by the square meters of BSA would exaggerate their differences rather than make them more comparable. Thus, the correct indexing method is to multiply (not divide) the calculated resistance by the BSA.

The same results would be obtained regarding indexing if the formula for estimating resistance included the use of pulmonary blood flow index in the denominator:

$$\frac{\overline{PAp} - \overline{PVp}}{Qp/M^2\ BSA} = \frac{(\overline{PAp} - \overline{PVp}) \times M^2\ BSA}{QP}$$

$$= \frac{(\overline{PAp} - \overline{PVp}) \cdot M^2}{QP}$$

For example, a patient with a mean pressure of 37 mm Hg in the pulmonary artery and 7 mm Hg in the PCW with a cardiac output of 1.0 L/min and a BSA of 0.33 M^2 has a resistance of 30 HRU as:

$$\frac{37 - 7\ \text{mm Hg}}{1.0\ \text{L/min}} = 30\ \text{HRU}$$

To index this, one should multiply by the BSA to get the correct value of 10 HRU·M^2 (30 × 0.33 = 10). However, if one divided the HRU by the BSA, the incorrectly calculated value would be 91 HRU/M^2.

INDICATOR DILUTION CURVES

In the 1950s and 1960s dye curves were the most common way of estimating cardiac output; they were equally important in de-

Table 54–13. "Irreversible" Pulmonary Hypertension

Reference	*"Irreversible Level"*	*Lesion*	*Hospital Mortality*	*Comments*
52	PA systolic pressure >80% of SA systolic pressure	VSD	26%	Surgery in 1956–63
53	TPR >6.6 mm Hg·min·L^{-1}	VSD	29%	Not indexed to surface area
57	Rp >8 units·M^2	Truncus arteriosus	39%	Two patients with Rp of 8.6 and 11.4 units·M^2 suddenly died late postoperatively of PVOD
57	Rp/Rs >0.6	Truncus arteriosus	54%	
58	Rp >12 units·M^2	Truncus arteriosus	100%	Same institution as reference 57 but 3 years earlier
61	Rp/Rs >0.75	VSD	54%	Rp/Rs of 0.45–0.75 had same survival rate as Rp/Rs of <0.45

Abbreviations: PA = pulmonary artery, SA = systemic artery, TPR = total pulmonary resistance, Rp = pulmonary vascular resistance, Rs = systemic vascular resistance, PVOD = obstructive pulmonary vascular disease, VSD = ventricular septal defect, TGA = transposition of great arteries.

COMMENTS: The term "irreversible level" is used to mean that at pressures or resistances greater than listed, the patients in the series who had surgery had a high incidence of surgical mortality from PVOD.

Mair et al. (reference 58) speculated that patients with truncus arteriosus who had a single pulmonary artery could have twice the pulmonary resistance (Rp of 20 units·M^2 or less) than patients who had a two pulmonary artery system. Newfeld et al. (reference 59) in a study of lung specimens of 200 patients with TGA found that those with an Rp <5 units·M^2 did not have PVOD while those with an Rp >10 units · M^2 usually did have PVOD. DiSesa (reference 60) found that in three patients with bidirectional shunts with elevated pulmonary artery pressures who had an Rp/Rs of <0.5 were successfully operated with a significant reduction in pulmonary artery pressure postoperatively and a similar reduction in Rp. Clarkson et al. (reference 62) studied autopsy material from 35 patients with TGA and suggested that corrective operations for TGA should not be performed unless the Rp is substantially less than 10 units·M^2.

tecting abnormal intracardiac shunts and valvular regurgitation. Until 30 years ago Evan's blue (T-1824) was the main indicator dye used. This dye had two main drawbacks: 1) It stained the tissues and was cosmetically unattractive causing the patient to have a slate blue coloration that lasted for up to two weeks depending on the dose used.[64] This discoloration would often disappear within half a week, but would reappear with exercise. It also provided difficulty in evaluating cyanotic patients after catheterization. 2) It has a maximal light absorption of 630 to 650 mu, which is the red region. At this range the reduced hemoglobin and oxyhemoglobin have enough difference in light absorptions so that any change in the ratio of the two hemoglobins (which is the oxygen saturation) affected Evan's blue dye curves.

Multiple other indicators have been used including: other dyes, hydrogen gas,[65] freon,[66] ascorbate,[67] nitrous oxide,[68] and radioactive agents.[69] At the present time these are essentially only of historical interest and are described well in Chapters 6 and 7 of Zimmerman's textbook.[70,71]

As we discuss indicator dilution curves in their historical perspective, it will become apparent why they used to be important. Measurement of cardiac output at the time required cumbersome methods for both collection of oxygen and measuring oxygen content. Indicator dilution curves were much more sensitive in detecting cardiovascular shunts than was oximetry.[72] Otherwise, left-to-right intracardiac shunts had to be detected by increases ("step up") of oxygen saturation and were not accurate below levels of 3 to 10% (see oximetry section) or a Qp/Qs of below 1.3 to 1.5/1. Currently, the problems of measuring cardiac output have been markedly improved with the thermodilution technique, measuring oxygen consumption by the polargraphic method, and oxygen saturations can quickly be measured by spectrophotometry.

Historically, earlier angiographic techniques and results were relatively poor compared to today's standards. Angiograms were often done without fluoroscopic visualization, as the equipment for taking radiographs was usually separate from the fluoroscopic unit. Usually only six radiographs were taken each second, and small shunts and mild valvular regurgitation were often not visualized. Now echocardiograms and angiography at 60 frames per second will detect almost any small intracardiac shunt. In fact, the images of individual cineangiographic frames at the present time are superior to the 6 frame per second regular size radiographs taken 25 years ago. For example, prior to present day cineangiography, determining whether or not a patient had a PDA by angiography usually required moving the patient and/or x-ray table and injecting contrast material "blindly" in the aorta to see whether or not a ductus was present. Injecting a dye in the aorta and discovering its immediate appearance in the pulmonary artery used to be a much easier way than angiography to determine if a PDA was present.

Indicator dilution curves enjoyed marked popularity in the 1960s with the introduction of indocyanine green as an indicator dye.[73] Indocyanine green did not discolor the patient. It also has a peak absorption at 805 NM where the light absorption of reduced and oxyhemoglobin are the same so that indocyanine green (which was also known as Fox green) was not affected by changes in saturation. In the 1970s the use of indocyanine green began to diminish, and now it is essentially used only for detecting right-to-left shunts. However, to understand the technique of how dilution works as an indicator we will now demonstrate some of the methods used in measuring cardiac output with green dye.

A green dye cardiac output determination can be compared to putting any material, such as a pollutant, into a river and measuring its concentration downstream. (This example is used because it demonstrates how a dye dilution curve works; it is not intended

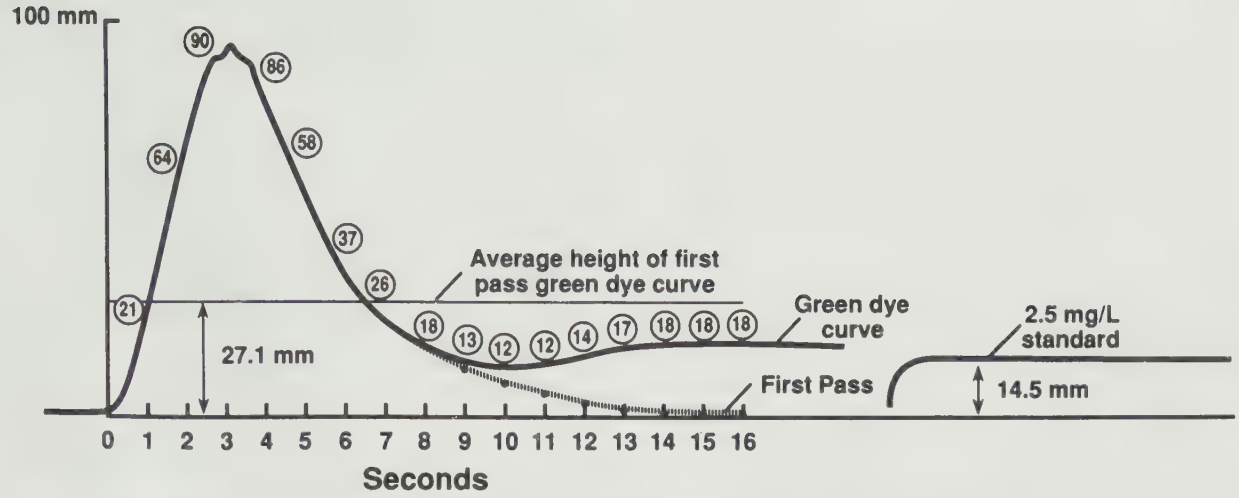


Fig. 54–13. Measurement of cardiac output with an indocyanine green dye curve: 5 mg of green dye was injected into the venous system and at time 0 it is detected by a densitometer. At about 3½ seconds the green dye curve peaks at a maximum of 93 mm (the numbers inside the circles are the height of the dye—in mm—each second). At 9 seconds the curve begins to rise a second time, due to recirculation of the dye. The dashed line is the curve that would have been inscribed if there were no recirculation; this is also known as the "first pass" of the green dye. Note that the standard, which was 2.5 mg of green dye per liter of blood, gave a standard curve height of 14.5 mm. Thus, the average height of the first pass of the green dye curve is 27.1 mm as discussed in Figure 54–14.

as a political statement, and does not necessarily represent the views of the publisher, editors, authors' institutions, or authors.) For example, let us assume that 2000 lb (16 oz per lb) of a toxic waste is dumped into a river and after complete mixing there is found to be exactly 1 oz of toxic waste in every gallon of water downstream. Thus, the 2000 lb of toxic waste had to have been diluted in 32,000 gallons of water. And if this bolus of toxic waste, which averaged 1 oz per gallon of water, completely passed by a measuring station in exactly 3 minutes and 12 seconds (3.2 minutes), then the river is flowing a rate of 10,000 gallons per minute. Measuring cardiac output is similar. A known amount of green dye is injected into the bloodstream, the concentration is measured downstream, and the time the green dye passes is also calculated.

However, in using the river analogy there is one major difference. This is due to the recirculation of blood, which is analogous to a city taking the polluted water at a point downstream, using it for drinking water, and then dumping it back into the river upstream. Now one could not determine how much of the toxic waste was due to the initial contamination and how much was due to the recycling. In measuring green dye curves, the same thing happens, some of the blood with green dye recirculates through the entire body and gets back to the measuring point (usually the femoral artery in children) before the initial bolus of green dye has passed downstream. Thus, in determining the cardiac output from a green dye curve, one must first determine which part of the curve is due to the first pass of the green dye and how much is due to recirculation. Because of the exponential decay of the disappearance of the first pass of green dye this can be determined by plotting the disappearance curve on semilog paper. Figure 54–13 shows a typical green dye curve and Figure 54–14 shows the semilog plot of the dye curve.

The technique of measuring the cardiac output by doing a green dye curve is to inject a known amount of dye, usually 5 mg, into the pulmonary artery, though it can be injected anywhere in the venous system. Then one continuously withdraws a constant flow of blood from the femoral artery into a densitometer cuvette capable of measuring the concentration of green dye in the blood. A green dye curve is inscribed as shown in Figure 54–13.

A calibration factor is then determined by diluting a known amount of green dye into a sample of the patient's blood. This is done by using a microliter syringe to inject the green dye solution into a 10-mL volumetric flask of blood (drawn before any dye is injected into the patient) so that the final concentration will be 2.5 or 5.0 mg of green dye per liter of blood. This sample is then withdrawn through the same densitometer cuvette and the height of the calibration line displaced from the baseline will be equal to 2.5 or 5.0 mg/L.

Green dye cardiac outputs are classically done by using the Stewart Hamilton equation which is[75,76]

$$CO = \frac{60 \times i}{\bar{c} \times t}$$

Using the values in Figures 54–13 and 54–14 we can see that over 16 seconds (t) the sum of all the measured heights in the initial pass of green dye came to 434 mm. Thus, the average height of the green dye curve during those 16 seconds was 27.1 mm. Because the calibration factor contains a height of 14.5 mm deflection for 2.5 mg/L, the average concentration of the green dye curve is 4.7 mg/L ($\bar{c}$). Since 5 mg of green dye was injected (i), the cardiac output comes to 4.0 L/min as shown in Table 54–14.

There are multiple formulas for calculating cardiac output from green dye curves.[1] All of them are based on calculating the area of the curve to determine the denominator in sec·mg/L. The most common other formula is

$$CO = \frac{60 \times i}{A \times CF}$$

As shown in Table 54–15 this is really identical to

$$\frac{60 \times i}{\bar{c} \times t}$$

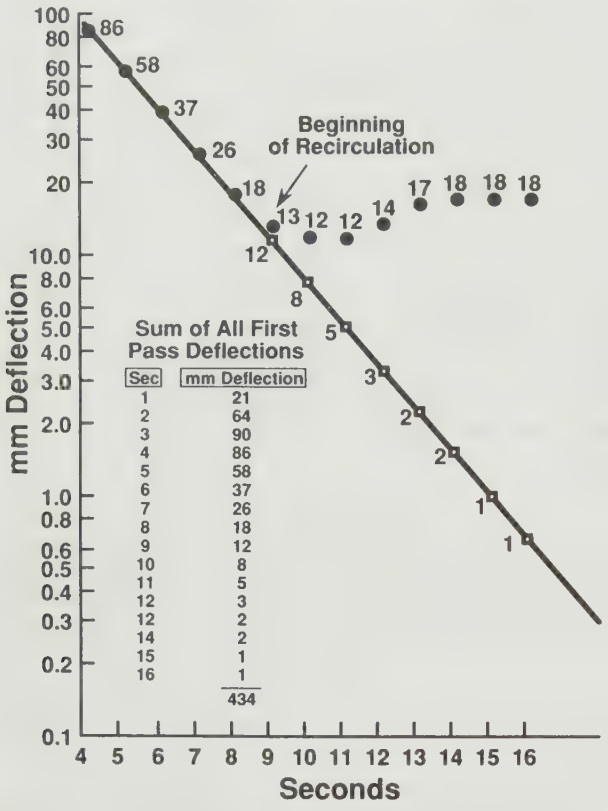


Fig. 54–14. Exponential decay of an indocyanine green dye curve: the disappearance of green dye from the circulation of the bloodstream decreases in an exponential fashion. If no recirculation occurred, the green dye disapperance curve would be a straight line on semilog paper. However, in most children about 10 seconds after the initial appearance of the first amount of green dye at the arterial sampling site, recirculation of blood (and hence the green dye) will occur. Thus, one plots the level of green dye on three cycle semilog paper. Where the straight line "breaks" is the beginning of recirculation. The straight line is then extrapolated to 1% of the peak concentration of green dye. The first pass of green dye is assumed to be completed when less than 1% of the initial first pass persists (which is in this case would be 0.93 mm, as the peak concentration was 93 mm). Next, one determines the average concentration of the green dye during the entire first-pass green dye curve. This is done by summing up the amount of green dye present during the first pass. In this example from Figure 54–13, during 16 seconds the sum of all of the first-pass deflections was 434 mm, which comes to an average height of 27.1 mm. The standard of 2.5 mg/L caused 14.5 mm of deflection. Since the first-pass green dye curve had an average height of 27.1 mm, the average concentration of the first-pass green dye curve would be 4.7 mg/L. Reference 74 and the previous page include further explanations of how to determine cardiac output.

There are also formulae where one can assume that the area of the initial portion of the curve is proportional to the total area of the curve. For example, in the forward triangle method of Hetzel, the initial portion of the curve corresponds to 35% of the total area of the curve following a peripheral injection of green dye, and 37% if a central injection is used.[77] The forward triangle method is the most common formula used for determining green dye cardiac outputs, because it is relatively easy to do and does not require determining the recirculation phase. See Figure 54–15 for an example of a cardiac output done using the forward triangle method.

With left-to-right shunts, low cardiac output, and valvular insufficiency; the cardiac output frequently cannot be determined by the usual formulae because in these conditions one often cannot determine where the recirculation phase begins. In these situations the forward triangle method is an alternative method that can be used for calculating cardiac output; with left-to-right shunts, it is debatable how accurate these alternative methods are.

There are potential errors in measuring the cardiac output from green dye curves. One main problem is no matter how accurately one tries, the amount injected through a syringe and catheter usually will not be exactly the amount thought to be injected. We use a stopcock system where the green dye is injected first and this is followed by a saline flush. We believe this method is as accurate as any of the multiple ways we have used to try to deliver accurate volumes of green dye. Another potential error is that the flow in the withdrawal syringe has to be constant, and, therefore must be

Table 54–14. Standard Formula for Calculating Cardiac Output by Indicator Dilution Curve

The formula for calculating cardiac output is

$$CO = \frac{60 \times i}{c \times t}$$

Abbreviations: CO = cardiac output in L/min, 60 = sec per min, i = mg green dye injected, c = mean concentration of green dye in mg/L, and t = seconds.

Therefore with the example in the text, the cardiac output is

$$CO = \frac{60 \text{ sec/min} \times 5 \text{ mg}}{4.7 \text{ mg/L} \times 16 \text{ sec}} = 4.0 \text{ L/min}$$

It can be seen that seconds and milligrams of green dye will cancel out so that the final units are L/min (liters of blood flowing per minute).

Table 54–15. Alternative Cardiac Output Formula (Denominator)

$$CO = \frac{60 \times i}{A \times CF}$$

Where A = area of first pass of green dye curve measured in mm deflection multiplied by duration of first pass in seconds; and CF = calibration factor of standard measured in mg green dye per L/per mm deflection.

Since "mm deflection" cancels out, A × CF have the same units in the denominator as $\bar{c} \times t$ which are mg/L × sec.

Using the data in Figures 54–13 and 54–14, and Table 54–14; the area of the curve is 434 mm deflection × sec during the first pass, and the calibration factor is 2.5 mg/L/14.5 mm deflection.

Thus, the formulae are

$$CO = \frac{60 \times i}{\bar{c} \times t} \text{ or } \frac{60 \times i}{60 \times CF}$$

and the calculations are $\frac{60 \times 5}{4.7 \times 16} = \frac{300}{75.2}$ or

$$\frac{60 \times 5}{434 \times \frac{2.5}{14.5}} = \frac{300}{74.8}$$

The differences are due to "rounding off," a more precise figure for "$\bar{c}$" is 4.677, which also gives 74.8 mg/L × sec in the denominator.

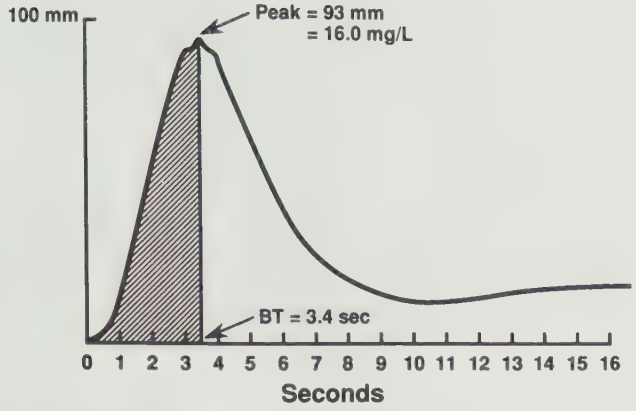


Fig. 54–15. Forward triangle method of Hetzel and associates:

$$CO = \frac{i \times 60 \times K}{\frac{PC}{2} \times BT}$$

where: CO = cardiac output in L/min

i = amount injected in mg

60 = 60 sec/min

K = constant of 0.37 or 0.35

PC = peak concentration in mg/L

BT = time in sec to reach peak concentration

This curve is the duplicate of the curve in Figure 54–13. It took 3.4 seconds to reach a peak deflection of 93 mm. 93 mm deflection is equivalent to 16.0 mg/L as 14.5 mm deflection = 2.5 mg/L. Therefore, using the forward triangle method, the cardiac output is 4.1 L/min.

$$CO = \frac{5 \times 60 \times 0.37}{\frac{16.0}{2} \times 3.4} = 4.1 \text{ L/min}$$

done by a constant infusion pump. The cardiac output has to stay constant during the measurement or the result will be incorrect. There has to be complete mixing of the dye and the blood, which usually means that the dye must pass through at least one ventricular chamber. The delayed curves that occur with valve insufficiency and low cardiac outputs cause inaccurate readings.

In general, the Fick principle is better for accurate determination of reduced cardiac outputs, and the green dye method is better when the cardiac output is increased. When the cardiac output is high there usually is a small difference between the arterial and venous oxygen content, so that any errors in measurement of AVO_2 difference will cause a proportionally large error in the calculated cardiac output when using the Fick principle. On the other hand, a low cardiac output will result in a significant portion of the initial bolus of the green dye recirculating before the first circulation is complete.

Approximately 10 years ago the thermodilution technique replaced green dye curves for measuring cardiac output. While green dye curves are still occasionally used for measuring shunt fractions, presently the only major remaining role of green dye curves is detecting small right-to-left shunts. For example, a patient may have a oxygen saturation of 93% in the femoral artery and two pulmonary venous samples could be 93% and 96%. In this case one could not tell by oximetry if a small intracardiac right-to-left shunt was present or not. Injection of green dye into the IVC with sampling in the femoral artery will reveal if there is early appearance of the dye in the femoral artery. If early appearance does occur with the green dye curve, then some of the mild desaturation of the femoral artery in this case was due to an intracardiac right-to-left shunt. Injection of green dye into the IVC with sampling in a systemic artery is one of the most sensitive methods available for the detection of a small right-to-left shunt. This is because fetal patterns of preferential blood flow from the IVC across the foramen ovale often persist in the child, even when there is no other right-to-left shunt present. A Valsalva maneuver will increase the right-to-left shunt across the foramen ovale.[78] Figure 54–16 shows examples of right-to-left shunts.

Green dye curves are essentially no longer used for detecting intracardiac left-to-right shunts or minor amounts of valvular regurgitation, because of the development of cineangiography and echocardiography. However, prior to the 1970s it was almost impossible by angiography to visualize mild amounts of valvular regurgitation when the angiograms were taken at only 6 frames per second. Also if atrioventricular valvular regurgitation was seen, one often could not determine whether this was due to "true" valvular regurgitation or to ventricular ectopy which usually occurred with ventricular angiograms. However, if injection of green dye into the left ventricle revealed early appearance of the dye in the left atrium, one could conclude that mitral regurgitation was present. First, these intracardiac curves (injecting dye in the heart

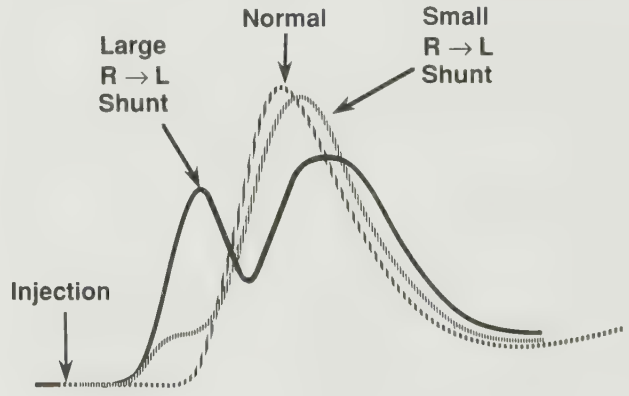


Fig. 54–16. Examples of right-to-left shunts: by injecting in the "right side" of the circulation and sampling in a systemic artery, one can detect a right-to-left shunt if there is early appearance of the green dye. Also, the contour of the curve with the early peak suggests that there is a right-to-left shunt. The greater the magnitude of the early peak, the greater the magnitude of the shunt. The site of a right-to-left shunt can be detected by injecting in two different right-sided chambers, with one of the chambers being distal to the shunt. For example, in a patient with right-to-left shunting at the atrial level, injection in the right atrium and sampling in the femoral artery would show an early peak to the dye curve, while injecting in the right ventricle and sampling in the pulmonary artery would show a normal curve without an early peak, thus confirming that the right-to-left shunting was at the atrial level.

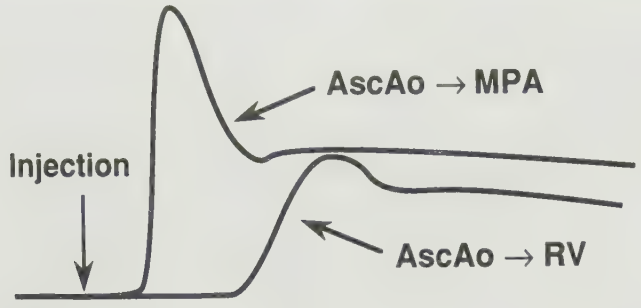


Fig. 54–17. Example of an intracardiac curve: "intracardiac curves" refers to using two catheters in the heart, injecting in one and sampling in the other. In this example, a patient with a patent ductus arteriosus (PDA), green dye is injected into the ascending aorta (Asc Ao) in both examples, but the sample is withdrawn from the main pulmonary artery (MPA) in one and from the right ventricle (RV) in the other. Note that there is an early appearing tall peak in the sample withdrawn from the MPA because relatively undiluted green dye is diverted directly from the Asc Ao to the MPA by way of the PDA. However, the green dye, which has to circulate through the body before it reaches the RV, is relatively diluted, so that the concentration of the green dye is much less.

with one catheter and sampling in the heart with another catheter) were very sensitive as essentially undiluted green dye would go directly from the left ventricle to the left atrium. Second, small injections of green dye rarely caused ectopy.

Intracardiac curves are also sensitive for finding small left-to-right shunts. For example, if one injects green dye in the left ventricle and finds early appearance of the dye in the pulmonary artery, but injecting in the left ventricle and sampling in the right ventricle does not show early appearance, then one could assume that the patient has a patent ductus arteriosus or some other type of left-to-right shunt at the great artery level. Figure 54–17 shows an example of an intracardiac curve.

Figure 54–18 shows examples of left-to-right shunts. Left-to-right shunts will have a lower peak than normal curves because some of the indicator recirculates through the lungs instead of going directly to the sampling point. There will not be as steep of a downslope, because the left-to-right shunt that recirculated through the lungs arrives at the sampling point later than the green dye that goes directly to the femoral artery.

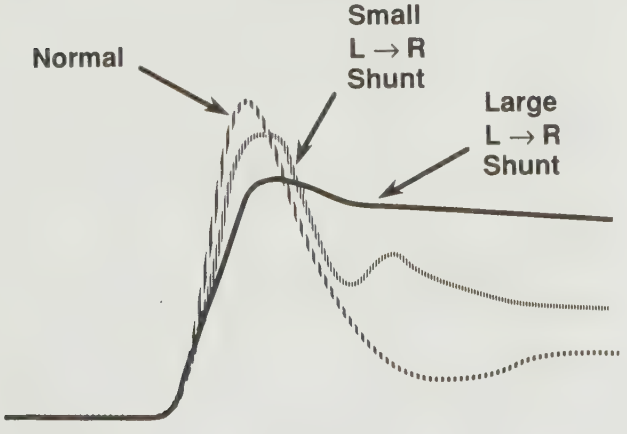
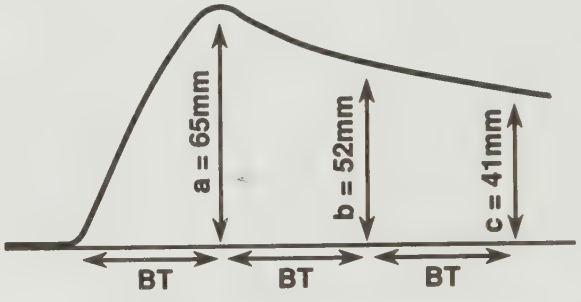


Fig. 54–18. Examples of left-to-right shunts: a large left-to-right shunt, compared to a normal curve, will have a slow decay of disappearance of the green dye at the sampling site. A small left-to-right shunt will have a curve similar to a normal shunt but will usually have a distinct early recirculation "bump." These examples are typical of injecting in the "right side" of the heart and sampling in a systemic artery.

Carter's formula has been developed for determining the amount of left-to-right shunting.[79] The Carter formula is best used when there is a smooth downstroke. If there is not a smooth downstroke, then the formulas of Victorica and Gessner should be used.[80] Left-to-right shunts by this method of green dye curve have a threshold of detection of about a 25 to 30% shunt.[81] Figures 54–19 and 54–20 show examples of left-to-right shunts and how to calculate the shunt fraction.

Figure 54–21 shows an example of calculating the percentage of a right-to-left shunt from a green dye curve where the dye is injected into the IVC and sampled in the aorta. As can be deduced, if blood or green dye passes directly from the IVC to the right atrium to the left atrium, it will arrive at the systemic artery much more rapidly than the normal blood flow would because it has to go from the right atrium to the right ventricle to the pulmonary artery to the lungs to the pulmonary veins and then back to the left atrium. Thus the early peak is due to the right-to-left shunt, and the magnitude of the early peak is proportional to the amount of right-to-left shunting. The formulas for calculating right-to-left



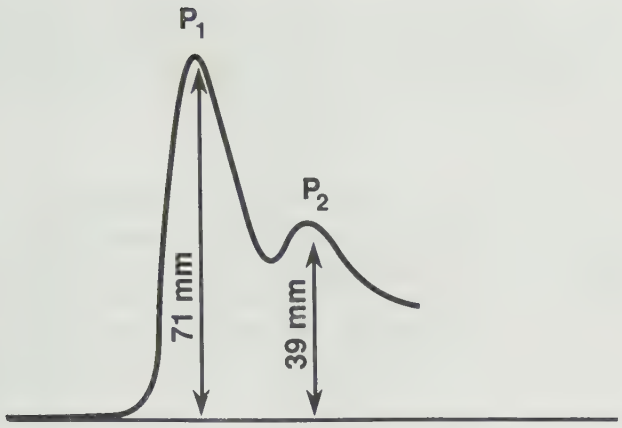
BT = time to reach peak concentration (build up time)
a = height of peak concentration in either mm or mg/l
b = height of dye curve at 2 BT
c = height of dye curve at 3 BT
%Qp = percent of pulmonary blood flow due to left to right shunt

formulae:

A. % Qp = 141 $(\frac{b}{a})$ -42

B. % Qp = 135 $(\frac{c}{a})$ -14

Fig. 54–19. Calculation of the amount of left-to-right shunting using the Carter formula: Carter and associates (reference 79) used arterial dilution curves to estimate the amount of a left-to-right shunt. "a," "b," and "c" can be measured in either peak concentration of milligrams of green dye per liter of blood or in millimeters deflection. In this example "a" is 65 mm tall (prior to being reduced in size for the text), "b" 52 mm tall, and "c" 41 mm tall. Thus for formula A, %Qp = 141 × (52/65) − 42 = 71%. For formula B, %Qp = 135 × (41/65) − 14, which also = 71%.



formula:

$$\text{A. \% Qp} = \left(\frac{P_2}{P_1}\right) \times 100$$

where:

%Qp = percent of pulmonary blood flow due to left to right shunt
P_1 = first peak
P_2 = second peak

Fig. 54–20. Two-peak method of calculating the amount of left-to-right shunting: Victorica and Gessner found that they could reliably estimate the magnitude of a left-to-right shunt if two peaks were present on the arterial dilution curve. They were usually able to show two discrete peaks if the indocyanine green was injected centrally and the blood was withdrawn rapidly from either the aorta or other central systemic artery. We have not generally found this to be true, but have not performed many green dye curves for determining left-to-right shunts since their article was published in 1975. The first peak (P1) is believed to be due to pulmonary blood flow. The second peak (P2) is believed to be due to the left to right shunt. In this figure the height of P1 is 71 mm and the height of P2 is 39 mm so that the percent of the pulmonary blood flow (%Qp) due to the left to right shunting is (39/71) × 100 which is 55%.

formula:

$$\text{\% Qs} = \frac{(BT_1)(PC_1)}{(BT_1)(PC_1) + (0.44)(T_2)(PC_2)} \times 100$$

where:

%Qs = percent of systemic blood flow due to R→L shunt
PC_1 = height of first peak
BT_1 = build up time from appearance time to PC_1
PC_2 = height of second peak
T_2 = time from injection to PC_2
0.44 = constant

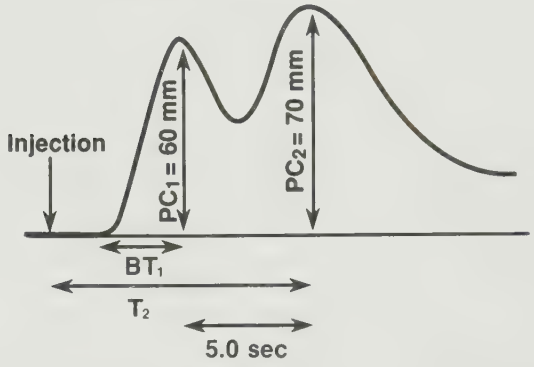


Fig. 54–21. Formula for calculating the amount of right-to-left shunting: using the above formula where PC_1 equals 60 mm deflection, PC_2 equals 70 mm deflection, BT_1 equals 3.3 seconds, and T_2 equals 10.5 seconds, the percent of the systemic blood flow which is due to right to left shunting is 38%. As shown by the calculation:

$$\%Qs = \frac{(3.3 \times 60)}{(3.3 \times 60) + (0.44)(10.5)(70)} = 38\%$$

shunts are modifications of the forward triangle method.[82] These methods will detect right-to-left shunts as low as 2.5 to 5% of the total cardiac output.[81] This increased accuracy probably reflects the fact that with right-to-left shunts the dye goes relatively undiluted (compared to the dye that must circulate through the lungs) and directly to the densitometer which is connected to the systemic artery.

THERMODILUTION

In the last decade, thermodilution has replaced indocyanine green as the main method of determining cardiac output. The advantages of thermodilution are 1) there is no recirculation phase because the cold water used for measuring the cardiac output is quickly dissipated by body temperature, 2) no blood needs to be withdrawn, 3) water is an inexpensive, inert, easily available indicator, 4) no arterial puncture is required (though we believe almost all children having cardiac catheterization performed should have an arterial line in place), 5) one can do rapid sequence determinations to obtain successive measurements, 6) cold water "mixes" somewhat better than green dye, 7) thermodilution is simple and easy to perform compared to the green dye technique, 8) because there is no recirculation, relatively simple computers can be used to measure the cardiac output rapidly, and 9) the amount of injectate used can vary and the computer will take this into account.

The technique of measuring cardiac output by thermodilution is to inject cold water in a proximal cardiac chamber and measure the temperature downstream. The method of using thermodilution catheters to measure cardiac output is first to position a specially constructed thermistor-tipped balloon-flotation catheter into the pulmonary artery or a PA branch. The thermistor is very sensitive to changes in temperature. The catheter has a proximal port for injection of cold water. The orifice of the proximal port will usually be in the right atrium or one of the vena cavae; this allows enough distance for complete mixing of the cold injectate with the blood. One then injects a known amount of iced or room-temperature water (or saline or dextrose solution) through the proximal port. As the cold injectate passes the thermistor, a computer that is connected to the catheter will calculate the cardiac output. In essence, the cooler the temperature of the blood as it passes the thermistor, the lower the cardiac output will be (i.e., when blood flow is low, then the cool injectate will not be diluted as much by the warm [body temperature] blood). It is also possible to "float"

the catheter out the aorta and measure the left ventricular output by sampling in the aorta after injecting in the left ventricle.

Either iced water or room-temperature water can be used for the injectate. We prefer using water at room temperature rather than ice water because it is easier to use. With iced water one can use smaller amounts. For measuring cardiac output, thermodilution is as accurate as using either the green dye method[83] or the Fick principle for determining cardiac output.[84] The thermodilution technique is also accurate for measuring cardiac output in children.[85]

Initially double thermistors were used for measuring cardiac output with one thermistor in the SVC to measure the temperature of the injectate and another thermistor in the pulmonary artery.[86] Now only a distal thermistor is used as the computers used calculate the injectate temperature. Use of a single thermistor requires the assumption that the temperature of the injectate is warmed a measurable amount during the injection. About 18% of the heat is lost in the handling process. Thus, the correction factor is 0.82,[87] for the difference between the temperature of the solution before it is injected and what the temperature is when it leaves the proximal port. This factor may be off depending upon the length of time that the physician holds the syringe in his/her hand and the time between injections. For infants we usually use 3 cc of injectate when measuring cardiac output, 5 cc for children up to 25 kg, and 10 cc for older children.

Cardiac output measurements should be done as rapidly as possible until three successive readings are within 15% of each other. In our experience they are usually within 5 to 10% of each other.

Thermodilution cardiac outputs are less reliable whenever there is a very low cardiac output.[88] This is probably due to heat loss during the prolonged time that it takes the cold water and blood to go from the injectate port to the pulmonary artery. Thus, the thermodilution method can overestimate the actual cardiac output whenever there is low flow.

Another possible error in the thermodilution technique can theoretically occur if the catheter thermistor happens to be against the pulmonary arterial vessel wall. In this case the temperature of the cold water bolus may be warmed by the temperature of the wall. This can give a falsely high cardiac output, but does not appear to happen very often if the catheter is not wedged. Thermodilution cardiac outputs are also unreliable if there is an intracardiac shunt. Though if the shunt (either right-to-left or left-to-right) is less than 10% of the total cardiac output, the error is usually insignificant.[89]

In both small and large left-to-right shunts, thermodilution measurements with the catheter tip in the pulmonary artery underestimate the cardiac output (Qs). If the left-to-right shunt is greater than 10%, one should use a different method for measuring the cardiac output. In a small right-to-left shunt, underestimation occurs because the thermistor, in essence, measures only the pulmonary blood flow and does not record that portion of the Qs that includes the right-to-left shunt. Because of the algorithm used in calculating the cardiac output, whenever there is a large right-to-left shunt, Qs can be highly overestimated.

With thermodilution, it is possible to measure bidirectional intracardiac shunts.[90] There is also a relatively simple method of measuring Qp/Qs in patients with a left-to-right shunt, and is calculated by a method similar to the way one measures left-to-right shunts from green dye curves.[91]

As long as blood flows freely, it does not appear to materially change the cardiac output whether one injects in the RA, adjacent IVC, or SVC; nor does it appear to matter if the thermistor is in the PA or its proximal branches (Fig. 54–22).

CALCULATION OF STENOTIC VALVE AREAS

The orifice size (cross sectional area) of a stenotic valve is calculated by using the Gorlin formula, which states that the pressure difference across a valve is directly proportional to the flow across the valve and inversely proportional to the area of the valve.[92] Obviously, the narrower the valve the greater the pressure gradient across it; similarly, the greater the flow across a narrowed valve, the greater the pressure gradient will be. The valve orifice of each cardiac valve is approximately 2.5 cm^2/M^2.

All one needs to calculate a valve area is 1) the cardiac output,

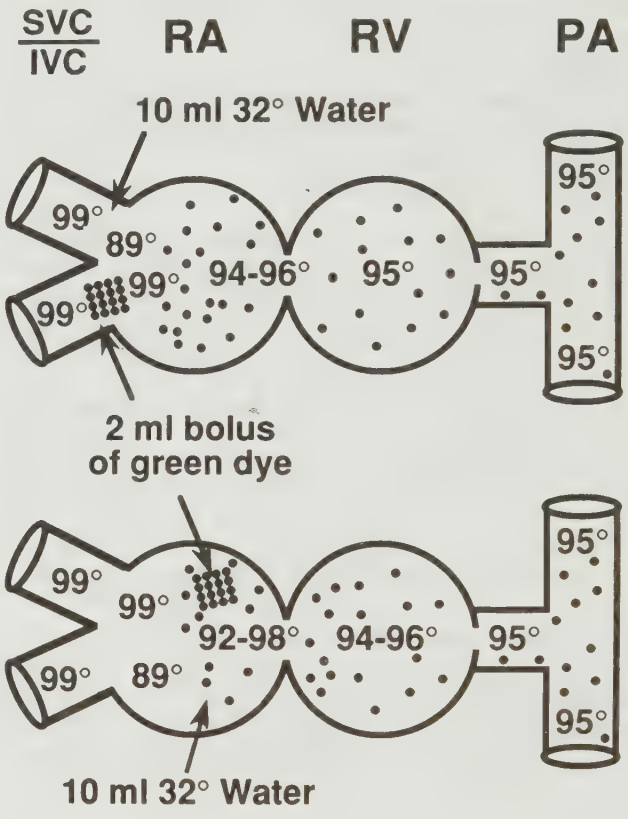


Fig. 54–22. "Mixing" of cold water, or green dye, in the "right heart": Abbreviations: SVC/IVC = superior and inferior vena cava, RA = right atrium, RV = right ventricle, PA = pulmonary artery and its branches. The numbers are the degrees in temperature Fahrenheit. The dots are particles of indocyanine green dye. In both panels the same amount of cold water (or green dye) is rapidly injected into the vena cava (upper panel) or right atrium (in lower panel). While there may be some temperature variation in the cardiac chamber distal to where the cold water was injected, by the time the cold water reaches the next chamber it should be essentially completely mixed. Essentially, the same principles apply to cardiac outputs obtained with injections of green dye. Note that for illustrative purposes the temperature changes by 4 degrees from the vena cavae to the PA; in actuality, the change in temperatures with thermodilution curves is much less than this (reference 83).

Table 54–16. Calculation of Aortic Valve Area by Gorlin Formula

$$AVA = \frac{\frac{CO}{SEP}}{C \times 44.3 \sqrt{LVP - AOP}}$$

Abbreviations: AVA = aortic valve area, CO = cardiac output, SEP = systolic ejection period. The SEP is the systolic ejection time (SET) multiplied by the heart rate (HR). C = correction factor, 44.3 = $\sqrt{2g}$. LVP = mean left ventricular systolic pressure, AOP = mean aortic systolic pressure.

See text for details. Note that the square root of the difference in the mean systolic pressures is multiplied by 44.3. This number is derived from the square root of the gravity acceleration factor (980 cm/sec/sec) multiplied by two.

2) the heart rate, and 3) the pressure curves from each side of the stenotic valve (along with the usual time lines and pressure calibration). In this section we will demonstrate how to measure the *aortic valve area,* as in pediatric patients this is the valve area most often measured, as the calculated valve area often provides information that is helpful in the decision regarding surgery. The Gorlin formula is shown in Table 54–16.

The first step in calculating the area of the aortic valve is to determine the mean gradient between the two pressure curves. This is done by measuring the area between the two pressure curves and converting this to a mean gradient in mm Hg. While the most accurate measurements are obtained by recording simultaneous pressures with high fidelity catheters in the left ventricle and in the aorta (and the average pressure gradient measured for three consecutive beats), in children this is frequently impractical or impossible. Most commonly, the left ventricular systolic pressure is measured using a large bore angiographic catheter. The femoral arterial pressure is measured simultaneously with the left ventricular pressure, however, there is a problem with pulse amplification and delay of the femoral pressure. In other cases the gradient is obtained by withdrawing the angiographic catheter across the stenotic valve; this makes it necessary to trace the aortic pressure curve and superimpose it over the left ventricular pressure.

The area between the aortic and left ventricular pressure is measured in mm² by planimetry. This area is then divided by its base in mm, to give a mean height of the area. The mean height difference in mm between the left ventricular systolic and aortic systolic pressures is then converted to a mean difference in mm Hg. This is shown in Figure 54–23.

Figure 54–24 shows two ways of estimating the average gradient. One way is to measure the difference in the pressure curves at 7 to 8 equidistant points along the curve. The sum of these pressures are added up and divided by the total number of lines as is shown on the right hand side of Figure 54–24. One can also estimate the mean pressure difference between the aortic and left ventricular tracings by estimating the mean of each pressure during ejection. Usually this estimate is within a few mm Hg of the actual planimeterized mean value and is demonstrated on the left hand side of this figure. The calculation of the pulmonic valve gradient is identical to the aortic valve gradient.

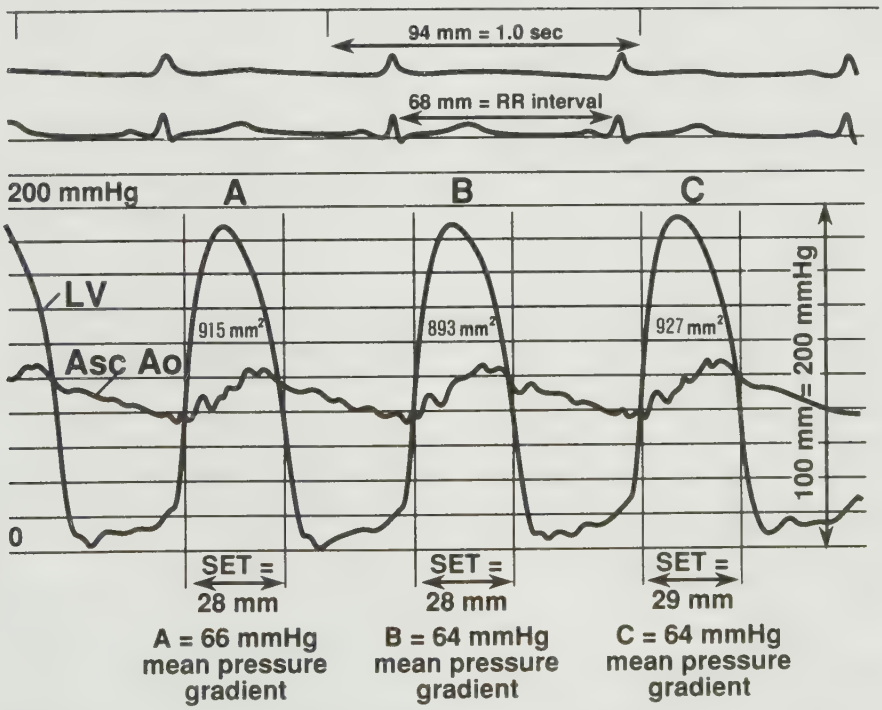


Fig. 54–23. Determination of aortic valve gradient using planimetry: in order to obtain an aortic valve area, one must first determine the mean pressure gradient between the left ventricle (LV) and ascending aorta (Asc Ao) during systole. This is done by using a planimeter to measure the area between the LV and Asc Ao pressure curve. The areas for curves "A," "B," and "C" are 915 mm², 893 mm², and 927 mm², respectively. The mean height difference between the two pressure curves is determined by dividing the area by the duration of the systolic ejection time (SET). This results in a mean height of 33 mm for "A," 32 mm for "B" and 32 mm for "C." Since 1 mm = 2 mm Hg the mean systolic pressure gradient from LV to Asc Ao is 66 mm Hg for "A," 64 mm Hg for "B," and 64 mm Hg for "C."

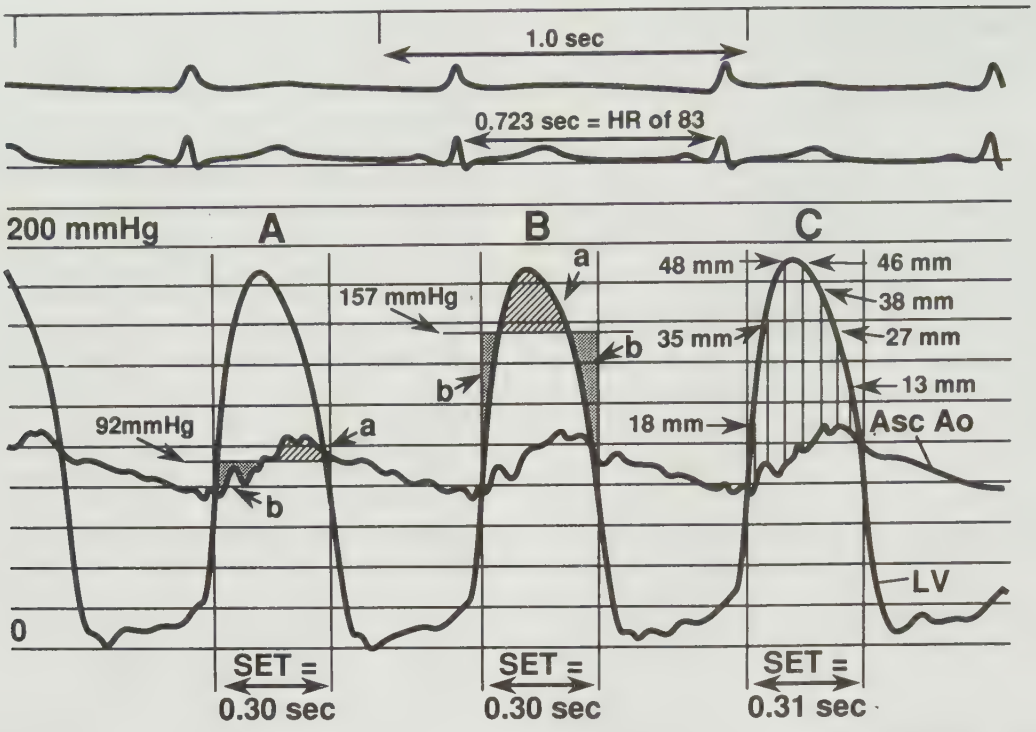


Fig. 54–24. This figure shows two ways of estimating the mean systolic pressure gradients between the LV and Asc Ao: these are the same pressure curves as shown in Figure 54–23. On the right hand side in "C," 7 equidistant lines are plotted and measured. The sum of the 7 lines is 225 mm. Therefore, the average of these lines is 32 mm. Since 1 mm = 2 mm Hg, the mean systolic pressure gradient is 64 mm Hg. Another way of estimating the difference in the pressure curves is to draw a line between both the Asc Ao and LV pressure curves *during ejection only* so that the area above the line ("a") is equal to the area(s) below the line ("b"). This is demonstrated in "A" and "B" and in this example does approximate the mean systolic pressure gradient very well (157 mm Hg − 92 mm Hg = 65 mm Hg). Also note that the heart rate (HR) and SET have been calculated in this diagram.

Table 54–17. Calculation of Aortic Flow (ml/sec)

$$Q = \frac{CO}{SEP} \text{ or } \frac{CO}{(SET) \times (HR)}$$

Q = flow (mL) each second the heart valve is open
CO = cardiac output in mL/min
SEP = systolic ejection period which is the number of seconds the valve is open each minute
SET = systolic ejection time which is the number of seconds that the aortic valve is open each heart beat
HR = heart rate which is the number of heart beats per minute

Therefore, the calculation of units is as follows:

1. $Q = \frac{CO}{SET \times HR} = \frac{mL/min}{(sec/heart\ beat) \times (heart\ beat/min)}$
2. "heart beat" cancels out and therefore:

$$Q = \frac{CO}{SEP} = \frac{mL/min}{sec/min}$$

3. "minutes" cancels out and therefore:

$Q = mL/sec$

Table 54–18. Calculation of Aortic Valve Area

Values for calculation are those in Figures 54–23 and 54–24, with the assumption for illustrative purposes that the cardiac output is 3000 mL/min:

Cardiac output (CO) = 3000 ml/min
Heart rate (HR) = 83 beats per minute
Systolic ejection time (SET) = 0.30 seconds per heart beat
Systolic ejection period (SEP) = HR × SET = 83 × 0.30 = 24.9 sec/min

$$Q = \frac{CO}{SEP} = \frac{3000}{24.9} = 120.5 \text{ mL/sec}$$

Mean gradient = 64 mm Hg

$$\text{Therefore, Cardiac output} = \frac{\frac{3000}{83 \times 0.30}}{1 \times 44.3\sqrt{64}} = \frac{120.5}{354.4} = 0.34 \text{ cm}^2$$

Note that the values used in this example are very similar to the text except that in the figures the heart rate was 83 instead of 80. Therefore the SEP was slightly more than in the text (24.9 vs. 24 sec/min) while the flow *each second* was slightly less than in the text (120.5 vs. 125 mL/min).

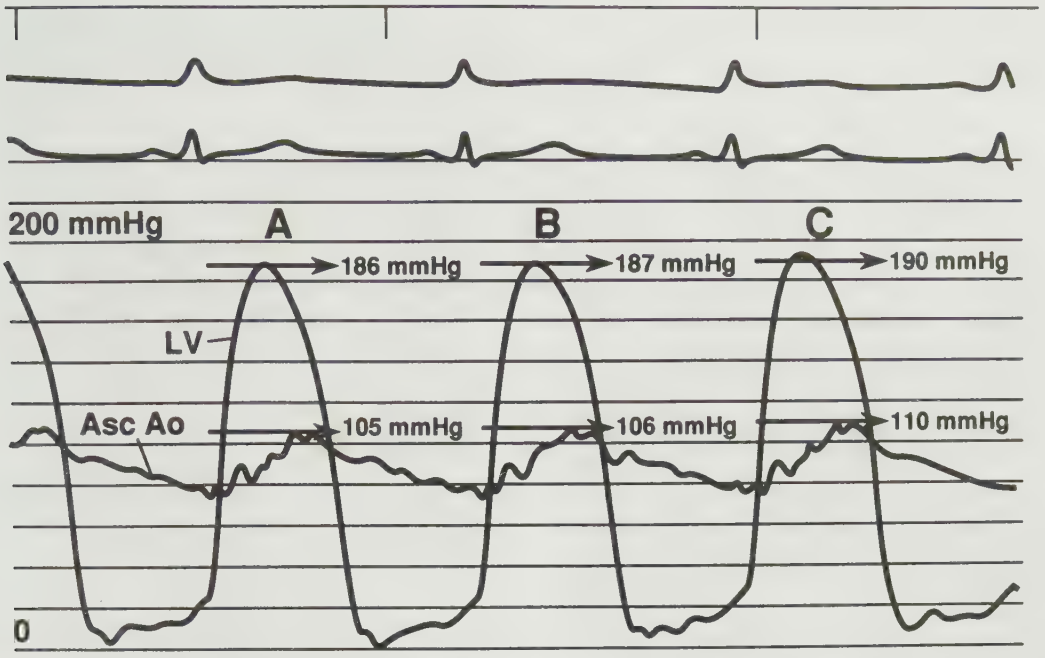


Fig. 54–25. Determination of the aortic valve area using the Bache method: the peak-to-peak systolic gradient is determined by subtracting the peak Asc Ao systolic pressure from the peak LV systolic pressure. The arrows represent the peak LV and Asc Ao systolic pressures for tracings "A," "B," and "C." Note that the differences for each of these three tracings is 81, 81, and 80 mm Hg; respectively. See Table 54–20 for the full calculation of the aortic valve area using the Bache formula.

After the gradient has been calculated, the flow across the aortic valve must be determined. In calculating valve areas one must use the flow that occurs when the valve is open. This is a different number than the cardiac output, and is determined by dividing the cardiac output by the time the aortic valve is open during systole.

Depending upon the heart rate and ejection time, systole occurs only about 40% of the cardiac cycle. Obviously, the aortic systolic gradient occurs only during the time that blood is flowing across the aortic valve. For example, if a patient had a cardiac output of 3000 cc/min, and had a systolic ejection time that was only 40% of the cardiac cycle, then the total of 3000 cc would be ejected only during 24 seconds of each minute. Thus, the flow across the aortic valve would be 125 cc each second the valve is open. This would correspond to someone who has a heart rate of 80 beats per minute with a systolic ejection time (SET) of 0.30 seconds. The systolic ejection period (SEP) is the heart rate multiplied by the SET; in the above example it was 24 seconds each minute. The SET is from the opening of the aortic valve during systole to its dicrotic notch. Table 54–17 shows how to determine the amount of blood flowing across the aortic valve each second which is the CO divided by the SEP.

For measuring diastolic flow across mitral and tricuspid valves, the diastolic flow period (DFP) is the diastolic flow time multiplied by the heart rate. As with aortic flow, mitral and triscupid flow is calculated by dividing the CO by the DFP. The diastolic flow time is from the opening of the atrioventricular valve to end-diastole. The gradient across the mitral valve is calculated similar to the aortic valve gradient, except that it is, obviously, measured in diastole.

The correction factor (C) is 1.0 for the aortic, pulmonic and tricuspid valves. In the initial report by Gorlin and Gorlin, 0.7 was used as the correction factor for the mitral valve. However, they did not measure the true diastolic time from actual pressure curves, but assumed them from systolic curves. Later on the correction factor for the mitral valve was changed to 0.85.[93]

Table 54–18 shows a calculation of an aortic valve area.

After reviewing the previous methods of measuring mean aortic valve gradients during systole, there is a shortened empiric formula for measuring the aortic valve valve area which requires using

Table 54–19. Example of Bache Formula for Aortic Valve Area (AVA)

$$AVA = \frac{Q}{37.8\sqrt{PSPG + 10}}$$

Q is the same as in Table 54–18 while the value for PSPG is from Figure 54–25, therefore:

$$AVA = \frac{120.5}{37.8\sqrt{81 + 10}} = \frac{120.5}{360.6} = 0.33\ cm^2$$

Table 54–20. Importance of Accurately Measuring Cardiac Output in Calculating Aortic Valve Area

A. $\frac{120.5}{44.3\sqrt{64}} = 0.34 = \frac{241}{44.3\sqrt{256}}$

B. $\frac{120.5}{44.3\sqrt{64}} = 0.34 = \frac{150.6}{44.3\sqrt{100}}$

only the peak-to-peak systolic gradient.[94] The formula is known as the Bache formula and is

$$AVA = \frac{\frac{CO}{SEP}}{37.8\sqrt{\text{Peak systolic gradient} + 10}}$$

An example is shown in Figure 54–25, and the calculations in Table 54–19.

Table 54–20 shows the importance of measuring the cardiac output accurately. The Gorlin formula states that if the flow is doubled, the gradient quadruples, assuming that the heart rate and systolic ejection time remain constant (which is not necessarily true). The example in Table 54–20 does reveal that a patient with an aortic valve area of 0.34 cm^2 will have a mean systolic gradient of 64 mm Hg with a flow of 120.5 mL/sec, but a gradient of 256 mm Hg with a flow of 241 mL/sec (almost an impossibility—but does show that doubling the CO will quadruple the gradient). Table 54–20 also shows that a 25% increase in CO (a definite possibility) will change the calculated gradient by more than 50%, from 64 mm Hg to 100 mm Hg.

There are errors in estimating the aortic valve area. In children probably the most important one is measuring the cardiac output simultaneously with the pressure measurements. This is usually not practical in pediatric patients as there is only so much time to do the study and only so many catheters that can be put inside a child's heart. There are also the inherent errors in measuring the cardiac output. When there is aortic regurgitation one also underestimates the area of the aortic valve because the measured cardiac output is less than the volume of blood that flows across the aortic valve.

Another error is using peripheral arterial pressures for the aortic pressure. The pressure curves do not line up with the aortic pressure because of delay in transmission of the pressure wave to the distal artery. Folland has shown that without realignment of the pressure curves, the left ventricular to femoral artery gradient overestimates the actual aortic valve gradient by about 9 mm Hg.[95] With realignment of the left ventricular and femoral artery tracings, the measured gradient underestimates the actual left ventricular to aortic gradient by about 10 mm Hg. Thus, the measured aortic valve gradient, the cardiac output, and hence the flow across the valve can be markedly different because they are recorded at different times, and under different physiological circumstances. This is especially true in pediatric patients when multiple sedatives frequently need to be given during the catheterization study.

How accurate are these valve gradients even if done as correctly and accurately as possible? The Gorlin formula is meant for rigid tubes without changes of the rate of flow. Flow across a stenotic valve is not uniform, and the stenotic valve may not be circular. With stenotic valves the opening of the valve may change in contour during systole. Furthermore, recent data suggests that the Gorlin correction factor (C) varies with the area of the valve, plus that the calculated valve area increases as the cardiac output increases.[96,97]

Despite these drawbacks, calculation of the aortic valve area is one more factor that can be used to decide whether or not the stenosis is severe enough to recommend surgery. In general, cardiac surgery is recommended when the aortic valve area is less than 0.5 to 0.7 cm^2/M^2.[98] This corresponds more or less to a peak systolic aortic pressure gradient of 50 to 75 mm Hg.

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CHAPTER 55

Catheterization and Angiography

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The role of cardiac catheterization in the management of cardiovascular disease has changed considerably over the past 20 yr, particularly in the past 5 to 10 yr in patients with congenital cardiovascular disease. These changes have been brought about by the development of new invasive and noninvasive diagnostic and therapeutic techniques.

Cardiac catheterization is no longer a "set piece" fishing expedition to make an anatomic and physiologic diagnosis. An experienced operator using high-resolution two-dimensional and Doppler echocardiography will be able to define most of the cardiovascular anatomy accurately in 95% of the patients with congenital cardiovascular defects.[1–3] Catheterization and angiography will be necessary only for patients with unusual anatomy, unusual presentation of common defects, or inadequate echo windows. The resolution of echocardiography does not yet approach that of angiocardiography; the need to obtain surgically important detailed anatomic studies will be decided by the cardiologists and surgeons treating a patient. The indications for cardiac catheterization in the management of some defects has decreased, while in others it has become the means for specific treatment (see Chapter 130).

At present, cardiac catheterization is the most reliable way to obtain data about the physiologic derangements caused by congenital cardiovascular defects. As the techniques for anatomic and physiologic correction of congenital heart defects continues to expand, there will be an increased need to evaluate the results as thoroughly as possible on a longterm basis; cardiac catheterization and angiography will continue to play an important part in ongoing evaluation of these surgical and medical treatments.

HISTORICAL BACKGROUND

Since its inception, cardiac catheterization has been used as an investigative and diagnostic tool by various disciplines in medicine and physiology. J.R. Dieffenbach[4] has been credited with the first use of a cardiac catheter in a human while treating a patient with cholera. Physiologist Claude Bernard[5] measured intracardiac temperature in animals, and in 1860 Pavy[6] coined the term "cardiac catheterism" to describe his experiences in passing a catheter into the right ventricle in humans and animals. A double-lumen catheter was used by physiologists Chauveau and Marey in 1861[7] to measure simultaneous pressures in the right ventricle and right atrium.

Werner Forssmann, using himself as the subject,[8] was the first to undertake a systematic study of the technique of cardiac catheterization and angiography. His early experiments were published in 1929 and 1931.[9] The first published works on central and peripheral angiography in children were published by Castellanos and his colleagues in Havana.[10–12] By the early 1940s, angiography of congenital cardiac defects was a well-established procedure.

The methodology and techniques of cardiac catheterization were standardized and extensively used by Cournand et al.[13] and others[14–17] in New York in the 1940s. There soon followed several papers and monographs[18–22] on the use of cardiac catheterization to diagnose congenital heart defects in children and infants. Catheterization of neonates was sporadic and little was published until the late 1950s[23,24] and 1960s when Adams and Lind,[25] Emmanouilides et al.,[26] and others[23,27] catheterized normal and sick infants to establish the foundations of our knowledge of fetal and neonatal cardiovascular physiology.

As surgical techniques for the repair and palliation of congenital

heart defects developed in the 1950s[28] and 1960s there were rapid developments and refinements of catheterization techniques, especially in younger children, infants, and newborns.[29–34]

Changes and improvements in surgical, imaging, and catheterization techniques have mandated a constantly evolving approach to the management of the infant and child with cardiovascular and pulmonary disease.[2,35] The application of these techniques will continue to change to supply the information needed for medical and surgical management of patients with congenital heart disease.

INDICATIONS FOR CARDIAC CATHETERIZATION

Table 55–1 lists the various diagnostic procedures and data that may be obtained during a cardiac catheterization. One should carefully evaluate the data that may be obtained by such procedures and whether it is applicable to the treatment of the patient. Not all of the procedures are a required part of a cardiac catheterization in a particular patient; one must formulate a protocol and design the catheterization procedure to obtain the most useful information in the least traumatic manner.

Cardiovascular Anatomy

The anatomy of the various parts of the heart and great vessels are demonstrated at cardiac catheterization using angiography and the course of the catheter through the heart and great vessels.[36] Before catheterization, a thorough two-dimensional echocardiographic study with Doppler will help plan the various angiographic studies (see Chapters 35 to 37). Two-dimensional echocardiography will provide accurate diagnoses of most of the above anatomic features under ideal conditions.[3] Echocardiography, however, is still an art, and the echocardiographer must be experienced in order to demonstrate, and more importantly to recognize, intracardiac and extracardiac anatomy. Demonstration of intrathoracic anatomy may be especially difficult in sick newborns with severe pulmonary disease, particularly those with emphysematous lungs, in whom an adequate echocardiographic window is difficult to find. In infants with severe hyaline membrane disease, anomalous connection of the pulmonary veins may be especially difficult to rule out,[35] and catheterization may be required for this single piece of information.

Table 55–1. Indications for Cardiac Catheterization

Define cardiovascular anatomy—The morphology, position, relations and connections of the
Systemic and pulmonary veins
Atria
Atrioventricular valves
Ventricles and outflow tracts
Proximal pulmonary and systemic arteries
Peripheral pulmonary and systemic arteries
Measure and calculate central and peripheral hemodynamics
Blood pressure in the systemic and pulmonary arteries and veins
Blood flow in the systemic and pulmonary circulation
Calculate shunts
Calculate vascular resistance in the pulmonary and systemic beds
Calculate valve areas
Evaluate cardiac pump function
Evaluate cardiac muscle function
Monitor changes in hemodynamics and cardiac function in response to drug, respirator, or surgical interventions
Electrophysiologic studies and therapy
Myocardial biopsy

Hemodynamics

Blood Pressures in the Central Aorta and Pulmonary Artery

The principles of data acquisition and wave-form analysis during cardiac catheterization have been well established and standardized for a number of years (see Chapter 29). Dynamic changes in the pulmonary and systemic circulations up to and for several months after birth[26,37] will determine what is interpreted as normal in a particular infant (Chapter 43).

In order to obtain accurate and reproducible blood pressure measurements, one should have a well-balanced and optimally damped transducer, which is matched to the catheter size and length of the connection tubing if a fluid-filled measuring system is used.[38–40] Catheters with side and end holes are preferable, with the widest, shortest path possible to the transducer. Great care should be taken when using small, balloon-directed Swan-Ganz catheters,[41,42] which have only an end hole; the small lumen size and relatively long length of these multilumen catheters usually produce over-damped pressure tracings. Other factors that may influence the accuracy and reproducibility of the pressure recordings are severe airway obstruction with marked inspiratory and expiratory swings in intrathoracic pressure and high mean airway pressure produced by respirator settings necessary for adequate oxygenation.

Physiologic Recordings

A minimum of four channels of simultaneous records should be available to record two electrocardiograms, and at least two simultaneous pressures. The pressure measuring and recording system should be evaluated before catheterization to optimize pressure signal recording. Small-caliber catheters will produce over-damped pressures in a fluid-filled system. Tubing length, caliber, and rigidity should be tested before the catheterization to minimize over- or under-damping.

Pressure wave forms are displayed and recorded at a gain to show the points of interest of the wave form in the middle of the screen. Each pressure recording is marked on the recording paper and in the handwritten log, and a calibration signal is recorded for each pressure.

The recording device may produce an instantaneous record for immediate viewing, but if photographic paper is used, it must be available for review immediately after the catheterization.

PRECATHETERIZATION ASSESSMENT

One of the most important parts of a catheterization is the prior assessment of the patient's clinical problems in order to decide which catheterization procedure is to be used. Catheterization procedures should be goal-oriented and be planned to elucidate further the nature of the patient's problem, as well as to set the background for future therapeutic maneuvers.

A complete physical examination and assessment of the patient's condition and stability is essential. A physical examination will identify the overall clinical condition of the patient, state of hy-

dration, cyanosis, respiratory distress, and adequacy of the peripheral circulation. Physical examination together with complementary laboratory investigations will determine whether the patient needs endotracheal intubation before the catheterization and whether other therapy such as inotropic support, diuretics, or prostaglandins should be started before catheterization.

An electrocardiogram is useful in evaluating arrhythmias, which may need to be controlled before the catheterization. The electrocardiogram can also reflect disturbances of electrolytes, pH, and blood sugar.[43]

Arterial blood gases indicate whether the pH should be corrected and if a trial of increased oxygen concentration will change the arterial pO_2. Any abnormalities of acid–base balance or electrolytes should be corrected as far as possible before the catheterization, as progressive acidemia and hypoglycemia often develops during catheterization of sick infants.[44] Hemoglobin and hematocrit should be measured before the catheterization, and blood volume or hemoglobin should be corrected as necessary using the arterial oxygen saturation value. The hemoglobin should be adjusted to produce an oxygen content of at least 15 mL of oxygen per 100 mL of blood (content = Hb g/dL × 1.36 mL O_2/g Hb × O_2 saturation). At least 20/mL/kg of blood should be typed and cross matched and available before the start of the catheterization.

A current two-dimensional echocardiogram is reviewed before the catheterization to evaluate the basic anatomy of the heart so that excessive use of contrast material is avoided. Anomalies of systemic venous return should be noted in planning the venous access route.[45–47] Echocardiography can define the basic anatomy of the heart and great arteries and help determine the need for further anatomic studies such as angiography. An echocardiogram is also useful in evaluating the contractility of the myocardium prior to the catheterization. The patency of the ductus arteriosus can be determined and can be monitored in response to prostaglandin administration.[47,48]

A written outline or plan of the catheterization procedures should be made so that none are omitted during the course of the catheterization and the laboratory staff can prepare for the various procedures.

PREMEDICATION

Most neonates do not require sedatives or narcotics before cardiac catheterization. Infants are particularly susceptible to the central nervous system depressant effects of narcotics; morphine, in particular, may destabilize the hemodynamics of an infant with low cardiac output by producing vagotonic bradycardia and venous dilation. Sedation of seriously ill patients should be administered under the direct supervision of the attending physician in the catheterization laboratory.

Meperidine (Demerol, 1.5 to 2.0 mg/kg), promethazine (Phenergan, 1.0 mg/kg), and chlorpromazine (Thorazine, 1.0 mg/kg) are commonly used in combination as an intramuscular "lytic cocktail" and given 30 to 45 min before catheterization. Chlorpromazine is a potent vasodilator, especially when given intravenously, and should be avoided in patients with ventricular outflow-tract obstruction, tetralogy of Fallot, and those with pulmonary vascular disease. Intramuscular injection of promethazine can be quite painful and oral administration of this drug or another antihistamine may be preferable. Diazepam alone given before catheterization to infants and small children does not provide enough sedation; it is a useful relaxant for older, more cooperative children.

Ketamine is a rapidly acting dissociative anesthetic and analgesic.[49] A dose of 2.0 mg/kg intramuscularly will sedate a child within 2 min. When given intravenously (0.5 to 1.0 mg/kg) over 30 to 60 sec there is no significant change in systemic or pulmonary hemodynamics. Moreover, it does not lower systemic resistance and therefore is an excellent sedative for patients with tetralogy of Fallot, who are likely to have a hypercyanotic spell. Slow administration into the pulmonary circulation does not produce vasoconstriction. Ketamine does not depress pharyngeal or laryngeal reflexes, and promotes salivation in patients who have not been given drying agents such as atropine or an antihistamine and in whom suctioning of the hypopharynx may produce glottic spasm. We recommend that ketamine be used only as an adjuvant sedative in combination with an antihistamine premedication.

TRANSPORT OF NEONATES TO THE CATHETERIZATION LABORATORY

The basic principles of neonatal transport as they are used in extramural transport should be applied to intrahospital transport.

The patient's hemodynamics should be as stable as possible and blood volume replacement should be completed before transport. Inotropic or other cardiovascular support drugs should be given at a stable infusion rate, with no adjustments required during the time of transport.

Intravenous lines should be secured and intravenous infusion pumps stabilized for safe transport. Prostaglandin infusions should be via a dedicated intravenous line; flushing of this line should be avoided because bolus injections of prostaglandins will cause apnea and hypotension.[50]

Body temperature control. An infant should be transported in a stable thermal environment such as an incubator or warming stand, as rapid heat loss can occur in an uncovered infant during transport through cold hospital corridors. Insulated wrappers are excellent for neonatal transport and are also radiolucent; the infant can be kept wrapped in this bunting during the catheterization with no degradation of x-ray quality.

Ventilator support. An intubated or ventilated patient is transported to the catheterization laboratory with hand-bagging by one operator. The patient's respirator or another respirator should be set up in the catheterization laboratory before transport so that it is ready to receive the patient on arrival.

Monitoring during transport. Electrocardiogram monitoring is all that is necessary during transport. An arterial line should be secured with a three-way stopcock and flush syringes during transport.

Arrival in the Catheterization Laboratory

Before the infant arrives the catheterization laboratory should be warmed to an ambient temperature of 80 to 85°F. An infant should be placed on some form of warming device. The warming device and the bunting, together with an infrared heating lamp, should be enough to keep the infant warm until being draped for the catheterization. Newer warming devices are not as radiopaque as older rubber heating pads; if heat loss is persistent the baby can

be sandwiched between two of the newer pads without significant loss of x-ray quality.

If a patient is ventilated a respirator must be easily accessible. Catheterization laboratory personnel should be drilled in a resuscitation routine so that obstructing x-ray equipment can be moved rapidly for access to the patient's head for respirator management and/or cardiopulmonary resuscitation.

Restraints are placed on the patient's arms and legs, even if paralyzing agents have been used, so that there will be no movement of the limbs or body after draping. The quality of respiration is assessed with a stethoscope after placing the patient on the catheterization table and the respirator connected. Adjustments to endotracheal tube position, with or without the use of fluoroscopy, are performed before the patient is draped, while there is adequate access to the head. Previously placed arterial lines are connected to the catheterization laboratory transducers and blood pressure and electrocardiogram evaluated for stability prior to starting any procedure.

Intravenous infusion sites should be inspected and should be available for visual monitoring during catheterization to guard against extravasation of fluid and drugs, particularly those containing calcium.

Monitoring During Catheterization

The heart rate, electrocardiogram, blood pressure, temperature, respiratory rate, respirator settings, chest movement, and air entry and infusion sites are monitored during the catheterization. Soon after the arterial line is placed, arterial blood gases are drawn to make sure that there has been no significant deviation from the previous values.

A respiratory therapist or physician is assigned to monitor the respirator, endotracheal tube, chest movement, and air entry during the catheterization. The position of the endotracheal tube, diaphragm movement and the presence of pneumothorax can be checked by fluoroscopy.

Central temperature is monitored via rectal probe with the monitor visible at all times. Excessive withdrawal of blood for blood gas measurements can be avoided by the use of a pulse oximeter placed over the toe, palm of the hand, or ear lobe for constant monitoring during catheterization. Blood sampling should be carefully monitored and excessive loss should be replaced with fresh packed red cells during the catheterization.

Two electrocardiographic leads are displayed, one for monitoring heart rate and one for diagnostic interpretation to observe the P waves and ST segments.

Monitoring urine output is important in patients with prerenal azotemia. A bladder catheter can be inserted or the diaper weighed prior to the catheterization.

Blood pressure can be monitored via an umbilical artery catheter, radial line, or femoral artery line. Marked fluctuations of blood pressure can occur during the catheterization due to infusions of drugs such as prostaglandin or after injection of hyperosmolar contrast material.

RIGHT HEART CATHETERIZATION TECHNIQUES

Catheter Insertion

The percutaneous femoral route is the preferred approach for diagnostic catheterization in patients with congenital heart disease. Percutaneous insertion of a sheath into the femoral vein is now a standard procedure and allows multiple catheter exchanges with minimal trauma to the vein.[51–55] Relatively large sheaths can be used even in small infants; for example, a No. 7 French sheath can be used to insert a balloon septostomy catheter in infants as light as 1.5 kg.

Both groins are infiltrated with 2% lidocaine over the site of needle entry and deeper over the site of vessel entry; convulsions may occur if the total dose of lidocaine exceeds 5 mg/kg.

Special short-bevel 21-gauge needles are used for easy insertion of guide wires. Longer-bevel needles tend to lacerate the vessels; blood return can be obtained with these needles even if the lumen of the needle is not completely within the blood vessel lumen. Guide wires of 0.018-in. diameter should be used for the initial insertion of a small No. 5 French sheath. If a larger sheath (No. 7 French) is to be used, a larger diameter guide wire (0.025 in.) is used for a better fit of the guide wire and dilator and greater stability of the dilator as it enters the vein at the pelvic brim. Short-bevel 19-gauge needles and 0.021- to 0.025-in. guide wires are used in patients heavier than 10 kg.

The femoral vascular sheath is approximately at the midpoint between the superior iliac crest and the pubic tubercle at the symphysis pubis in infants and children and at the medial one third of this line in adolescents and adults. Vessel entry is just below the inguinal ligament in infants and about 1 to 2 cm below this in larger children. The femoral vein and artery are impaled by the needle on the superior ramus of the pubic bone, where their position is relatively fixed and more superficial. The needle enters the skin at a 30- to 45-degree angle and is advanced a few millimeters at a time until blood appears in the hub or the pubic ramus is reached; if blood return is not obtained, the needle is withdrawn in 2- to 3-mm steps, with rotation of the hub at each step until blood is seen in the needle hub. If the vessel is not entered, the needle should be withdrawn and flushed to remove clots or tissue. Once blood return is observed, the soft end of the guide wire is advanced to the end of the needle and gently advanced into the vessel. If the wire does not advance immediately, the needle is advanced or withdrawn 1 to 2 mm and rotated while probing with the wire. Arterial entry of the wire should be very smooth; forceful entry will result in dissection, spasm, or clotting.

If the venous guide wire enters the femoral vein and does not advance beyond the pelvis, the needle is withdrawn over the wire and replaced with a plastic cannula. The wire can then be manipulated or withdrawn and curved. A guide wire should not be withdrawn from the needle once it has passed beyond the needle tip, as the soft floppy end of the wire may be shorn off.

When the guide wire has been advanced well into the inferior vena cava near the right atrium, the needle is withdrawn and pressure is applied to the puncture site; a small shallow nick is made in the skin with a number 11 scalpel and a 21- or 18-gauge tapered plastic cannula is passed over the wire to dilate the skin puncture and vein. This is particularly important during arterial puncture to facilitate smooth entry of the arterial dilator and sheath. The sheath is threaded over the guide wire and advanced into the vessel with a drilling motion, while slight tension is applied to the wire to avoid kinking in the subcutaneous tissue or vessel. A hemostasis valve can be placed on the end of the sheath to minimize blood loss during catheter exchanges.

The umbilical vein can usually be quickly cannulated and is often patent up to a week after birth.[56] To avoid prolonged probing

of the umbilical vein and the portal veins, a small injection of contrast material after insertion of the catheter will demonstrate whether the ductus venosus is still patent. A No. 5 French sheath and dilator can be passed over a guide wire through the ductus venosus in a similar fashion to femoral vein cannulation. The sheath prevents spasm of the ductus venosus if catheter changes are necessary. Intracardiac manipulation of the catheter from the umbilical vein is more difficult as the catheter lies posteriorly in the right atrium, and it is often difficult to enter the tricuspid valve and right ventricle from this approach. It is relatively easy to enter the left atrium and left ventricle from the umbilical vein, and this is a useful route from which to perform balloon atrial septostomy fairly quickly.

The brachial or axillary approach can be used if the femoral veins are not accessible.[57] The axillary vein can be punctured percutaneously about 0.5 to 1.0 cm below the distal axillary crease. The vein usually lies medial to the axillary artery, but the position can be variable. There is a greater risk of damaging the brachial plexus or axillary artery with a percutaneous approach because of lack of supporting subcutaneous tissue. If the axillary approach is necessary, it may be more expedient and safer to perform a cutdown just distal to the distal axillary crease. The vein or artery can be cannulated with a needle and guide wire under direct vision to avoid incising these small vessels.

The anterior brachial vein can be entered percutaneously or by cutdown, but in small neonates and premature babies this is usually too small to accommodate even a No. 5 French catheter, and there is a greater risk of spasm of the brachial vein; it is more difficult to manipulate the catheter through the long course from the arm to the superior vena cava.

The right internal jugular vein can be entered percutaneously[58] and a relatively large sheath can be placed into the superior vena cava. This approach requires a very cooperative or heavily sedated patient. Catheter manipulation from the jugular vein may be more difficult for operators accustomed to the femoral approach. A flow-guided balloon catheter is useful for this approach.

Vascular Cutdown

Incisional exposure of vessels for catheter entry has virtually disappeared from pediatric catheterization laboratories. This approach may be necessary after prolonged fruitless puncturing in a sick patient. The saphenous vein lies 1 cm medial and superficial to the femoral vein until it turns laterally through the deep fascia to enter the femoral bulb. In infants the incision is made through the femoral crease to expose the bulb, while in older children the incision is made 1 to 2 cm below the crease. The saphenous vein lies in the subcutaneous fat and can be traced cephalad to find the femoral bulb if femoral vein entry is desired. The femoral vein proximal and distal to the bulb should be freed with blunt dissection and looped with thick catgut or silk sutures for stability and hemostasis. The femoral artery lies immediately lateral to the vein, has a thicker pale wall, and may pulsate; the artery should be identified before the vein is entered. The artery and vein can be punctured with a short-bevel needle and a guide wire and sheath advanced in a manner similar to percutaneous entry. To incise the vein, a cut is made transversely with fine-pointed scissors and a second incision is made perpendicular to the transverse incision for 3 to 4 mm to make an inverted T. Large catheters or sheaths can be inserted through such an incision (Bargeron, L.M., personal communication, 1972). Incision of the vessel requires repair or ligation; after needle and wire entry, compression of the femoral sheath after skin closure will secure hemostasis.

Cutdown to the axillary vein is made through the distal axillary crease. The vessels and brachial plexus are below the superficial fascia, just medial to the long head of the biceps. Once again, one should identify both the vein and the artery before any vessel incision.

Catheter Types

Woven Dacron catheters are optimal for catheterizing patients with congenital cardiac defects because they are easier to control and direct. Softer, flow-guided balloon catheters are less traumatic but have much less torque control; in small babies the balloon size itself can be obstructive and limit catheter manipulation. While the balloon usually travels with the blood flow, this is not always where one wants the catheter to go. Small catheters such as a No. 4 French Dacron catheter or a No. 4 French balloon-guided catheter have very small fluid lumens, and pressure tracings are usually over-damped and the catheters can clot very quickly. Recent improvements in small catheter design have improved the usefulness of No. 4 French catheters for angiography.[59,60]

Catheter manipulation should be performed very carefully, conceiving the catheter as an extension of the finger with tactile feedback from the catheter tip. In newborn and premature babies, the myocardium is very soft, without much tactile feedback through the catheter. The myocardium is easily perforated, especially the medial wall of the right atrial appendage, which is very thin with little muscle. Perforation of the ventricle is especially likely with a dilated right ventricular outflow tract. There is often a diverticulum-like pouch just proximal to the pulmonary annulus, which appears to be more cranial than the pulmonary artery itself in the posteroanterior projection; forcible manipulation of the catheter in this position can result in perforation of the right ventricular outflow tract. When the anatomy of the heart is uncertain, small injections of 0.5 to 1 mL of contrast material will outline the anatomy enough for safer catheter manipulation and advancement.

Hemodynamic measurements are performed with an end-and-side-hole catheter for higher-fidelity pressure recordings and also to reduce the likelihood of clotting. After blood sampling and hemodynamic measurements are made, a fresh, clean angiographic side-hole catheter is used to perform angiograms.

In small hearts, manipulation of a catheter by itself, even with a balloon, can be difficult and traumatic. Guide wires may be used to help manipulate or bend the catheter,[52,53] especially to gain access to the left ventricle from the left atrium. Prolonged use of guide wires, even polytef (Teflon)-coated guide wires, can result in thrombosis of the catheter lumen[61]; wires should be used sparingly and catheters carefully aspirated and flushed after the use of guide wires. Guide wires with preformed tight curves are difficult to pass through small catheters and may result in loss of the curve. The use of a deflector wire and handle is helpful, and avoids the passage of a tightly curved wire into a relatively straight catheter. The deflector wires are manufactured with a tight 5-mm or larger 10-mm curve. They are particularly useful in entering the left ventricle from the left atrium in infants.

LEFT HEART CATHETERIZATION AND ARTERIAL CANNULATION

Arterial Cannulation

Systemic blood pressure is monitored through an 18- or 21-gauge polyethylene femoral artery catheter. Retrograde catheterization is performed at the end of the procedure to minimize the time that a catheter is in the artery.

When the arterial pulse is impalpable, arterial access can be facilitated by the use of a small Doppler probe over the groin to locate the site of the artery.[62] Continuous Doppler monitoring of the arterial pulse can be used as an early warning of arterial compromise.[63]

The umbilical artery can usually be cannulated in an infant less than 5 days of age.[56] In small infants, or when there is spasm of the artery, a small No. 3.5 French umbilical artery catheter can be used initially. The umbilical artery can be further dilated with a No. 5 French feeding tube or catheter to allow passage of a larger angiographic catheter. We have used the umbilical artery to insert a 5-mm balloon catheter for dilation of a coarctation. If the umbilical artery or vein is not accessible from the umbilical stump, a cutdown can be made at the base of the umbilicus to locate the vein or artery.[64]

Left Ventricle

We prefer the transseptal puncture with a long sheath technique[65,66] to enter the left atrium and left ventricle when the atrial septum is intact, even in small infants, of whom 12% may have an intact interatrial septum at under 1 yr of age.[67] This technique is used in preference to retrograde arterial catheterization to enter the left ventricle, as it avoids traumatizing small arteries and allows use of a larger, shorter catheter for left ventriculography. The long sheath can also be used to place other catheters and bioptomes into the left ventricle. Transseptal left atrial catheterization has been performed in infants as light as 1.5 kg.

Transseptal Left Heart Catheterization

The Mullins long transseptal sheath, dilator, and Brockenbrough needle are flushed with heparinized saline solution and assembled. The small 21-gauge needle tip should protrude 3 to 4 mm from the beveled dilator tip; the sheath is advanced to the end of the dilator and a note is made of the distance separating the hubs of the sheath and dilator, usually 3.5 to 4.0 cm. A 0.025-in. guide wire is passed through the femoral venous sheath to the high superior vena cava or innominate vein. The right femoral vein is the preferred approach for better apposition of the curved Brockenbrough needle and the atrial septum. If the left femoral vein is used, the patient may have to be rotated from left to right to tilt the atrial septum toward the laterally displaced needle. The dilator and sheath assembly are exchanged for the regular venous sheath over the guide wire and advanced to the superior vena cava. After withdrawing the wire and aspirating the dilator, the Brockenbrough needle is advanced to within 5 mm of the dilator tip. The needle is connected to the pressure monitoring tubing and the monitor gain is set to see the anticipated left atrial pressure in the middle of the screen. The directional arrow on the needle hub is directed posteromedially about 30 degrees below the horizontal plane, and the whole assembly is withdrawn as a unit until the dilator tip drops into the right atrium. A few premature atrial contractions may be noted. Continued withdrawal of the transseptal set may result in the tip dropping into the fossa ovalis; if this is not observed, the dilator tip is positioned low in the right atrium, about one vertebral body above the right hemidiaphragm, pointing toward the left and slightly posterior about 15 degrees.

The right atrial pressure wave may disappear when the dilator tip rests against the septum. When the position of the dilator is felt to be satisfactory after viewing the posteroanterior and lateral projections, the needle is advanced into the septal wall. Firm, steady pressure is applied to the assembly and the needle is usually felt to "pop" into the left atrium. If a left atrial pressure wave form is not immediately seen, a small injection of contrast material through the needle will outline the left atrial roof and posterior wall; incomplete entry is identified by a small plaque or "tag" in the atrial septum. Aspiration of the small-bore Brockenbrough needle is difficult and will cause clotting and loss of the pressure wave.

When the needle tip is free in the left atrium, the needle, dilator, and sheath are advanced as a unit toward the left shoulder until the dilator and sheath move across the septum. Some resistance may be felt as the sheath bevel encounters the septum, with bowing of the needle and dilator and lifting of the atrial septum toward the atrial roof. The presence of an undamped left atrial pressure wave form indicates that the needle tip has not reached the atrial wall and further pressure may be applied to advance the sheath through the septum. When the sheath has passed through the septum, it is pushed forward over the dilator 3 to 4 cm, where the almost radiolucent sheath tip is level with the more radiopaque dilator tip. Loss of the left atrial pressure wave indicates that the needle or sheath has reached the atrial roof.

With the sheath well in the left atrium, the needle is withdrawn from the dilator and the dilator is withdrawn from the sheath while aspirating blood to fill the sheath and exclude any air. The sheath is flushed and is ready to accept a catheter.

Retrograde Left Heart Catheterization

Retrograde arterial catheters are generally smaller and longer than venous catheters, which limits the amount and speed of contrast injections. Improvements in catheter design and material have resulted in smaller (No. 3.2 and No. 4 French) catheters,[59,60] which deliver sufficient amounts of contrast material at a fast enough rate for adequate opacification of the heart chambers and great vessels in infants with a rapid heart rate and high cardiac output. These catheters have less torque control than larger catheters. Newer formulations of catheter material have resulted in less kinking of these catheters during manipulation but they should be inserted and advanced with a guide wire. They are best used for retrograde aortic and left ventricular angiography where little catheter manipulation is required.

If it is anticipated that a retrograde catheter will be in place for longer than 20 to 30 min[68] systemic heparinization at 50 units/kg should be instituted. Routine heparinization for all retrograde catheterizations has been recommended by some authors.[69,70]

IMAGING

Biplane fluoroscopy and cineangiography are essential for optimal catheterization of infants and children with congenital cardiovascular defects. Magnification fluoroscopy in the 5- or 6-in.

mode is necessary for small infants; a small focal spot of at least 0.6 mm is required for optimal resolution. A high-quality videotape or disk recorder is necessary to immediately review angiograms to avoid unnecessary repeat angiography. Cineangiograms should be developed and viewed immediately after the catheterization, as the resolution of cineangiograms is higher than most currently available video-recording systems. Small details not visualized on the video recorder may become apparent when the developed film is viewed.

Two-dimensional echocardiography with Doppler facility is a useful adjunct to imaging in the catheterization laboratory. Contrast echocardiograms can localize shunting in any direction and have virtually replaced green-dye curves for shunt detection in my laboratory.

ANGIOGRAPHY

Angiocardiography is used to define the anatomy of the heart chambers and great vessels of the thorax. It is also used to visualize peripheral vessels in the systemic and pulmonary circulations to define the anatomy of the blood supply to various organs as well as the internal architecture. Blood flow between vessels (shunts) can also be demonstrated and ventriculography is used to assess regional and global function of the right and left ventricles. Because of the as yet unsurpassed detail and resolution that can be obtained by angiocardiography, this method of cardiac imaging is still the gold standard by which all other imaging techniques are judged.

The details of x-ray generation, dosage, image acquisition, processing, storage, and viewing will not be discussed here because of the constantly changing technology and equipment in these fields. These subjects are covered adequately in other sources with special reference to pediatric radiology.[71–75] The radiographic requirements for suitable imaging of pediatric patients with congenital heart defects are different from those required to image coronary arteries and the adult ventricle.

For angiography of the heart, one should try to fill the image-intensifier field with the heart or tissue of similar density. A fine focal spot of 0.6 mm or less is used for sharp definition; high kilovoltage and low milliamperage are used for maximal penetration and a wide grade scale. For viewing blood vessels, lower kilovoltage and higher milliamperage are used for sharper contrast and edge definition. The standard cine film format in pediatric laboratories is 35-mm film exposed at 30 to 90 frames per second using a fine-grain, wide-latitude film. Whenever possible one should use matched components along the whole imaging chain from the electrical generator to the x-ray tube, image intensifier, the cine camera, and video viewing system. Video-recording equipment should be of high resolution and allow storage of two to three cine runs, and have stop-frame viewing and flicker-free forward and reverse controls so that cineangiographs can be reviewed immediately after the injection is completed.

ANGIOGRAPHIC CONTRAST MATERIAL

Contrast material is radiopaque by reason of its iodine content, which ranges from 260 to 480 mg/mL in commonly used formulations. These materials are water soluble, iodinated salts of benzoic acid, while the cation is sodium or methylglucamine in various combinations[75] (Table 55–2). Sodium salts have a lower osmolarity and are less viscous but produce more toxicity and irritation, possibly in relation to its effect on ionized calcium.[76] The methylglucamine salts are more viscous, and the hyperosmolarity produces most of the cardiovascular side effects. Newly developed nonionic contrast materials have lower osmolarity and toxicity while producing opacification equivalent to the standard ionic contrast materials. Another ionic contrast material that has recently been developed is a dimeric benzoic acid derivative with increased iodine concentration at a low osmolarity and toxicity.[74]

Cardiovascular Effects of Contrast Material

The cardiovascular effects of contrast agents are related to the osmolarity, sodium content, and effects on serum calcium. In pediatric ventriculography, the usual dose of contrast material is between 1 and 2 mL/kg injected over two to three cardiac cycles, or about 1 to 2 sec (Table 55–3). This produces a slight immediate increase in ventricular end diastolic volume equivalent to about 50 to 60% of the normal stroke volume. If the injection is of a relatively large volume in a short period of time, there is an immediate increase in end diastolic volume and pressure with a Starling reflex increase in stroke volume, dP/dT, and ejection fraction, with a resulting rise in systolic pressure during the first two to five beats after the injection. However, with slower ventricular injections, during the first two to six beats, there is essentially no change in left ventricular dynamics and volume so that calculations of ventricular volume and function are comparable to the resting or preinjection state.[77–82] The pressure generated by the injector pump is not transmitted to the ventricular cavity and plays no part in the rise in end diastolic pressure during the injection of contrast material; the pressure from the pump is dissipated by the length and diameter of the catheter and the viscosity of the contrast material. Measurements of ventricular pressure with high-fidelity pressure transducers in the ventricle during injection show no change in systolic pressure during the injection.

When contrast material reaches the coronary circulation, there is coronary vasodilation and chelation of calcium from the blood

Table 55–2. Angiographic Contrast Agents

Name	*Type*	*Example*	*Iodine, mg/mL*	*Sodium, mg/mL*	*Osmolality*	*Viscosity at 37°C*
Diatrizoates	Ionic	Hypaque 75	385	9.0	2108	8.3
Ioxaglate	Ionic dimer	Hexabrix	320	3.48	600	7.5
Iohexol	Nonionic	Omnipaque	350		844	10.4
Iopamidol	Nonionic	Isovue	400		796	9.4
Metrizamide	Nonionic	Amipaque	300		484	6.2

Table 55–3. Dose of Contrast Agents

Site of Injection	*Dose (mL/kg)*	*Rate of Injection (mg/kg/sec)*
Ventricle, normal size	1.0–1.25	0.5–1.0
Ventricle, large, increased flow	1.5–2.0	1.0
Ascending aorta, MPA, normal flow	0.8–1.0	1.0–1.5
Ascending aorta, MPA, increased flow	1.5–2.0	1.5–3.0
Descending aorta, RPA, LPA	0.75–1.0	1.0
Pulmonary arterial wedge	0.5–1.0 (total)	0.25 mL/sec
Pulmonary venous wedge	0.3–0.6	0.5 mL/sec

MPA = Main pulmonary artery; RPA = right pulmonary artery; LPA = left pulmonary artery

and probably the intracellular fluid.[83,84] There is a drop in the coronary hematocrit due to an increase in intravascular water from the tissues. These effects result in decreased myocardial contractility with a rise in end diastolic volume and pressure and a decrease in stroke volume, depending upon the initial contractile state of the ventricular myocardium. Patients with coronary artery disease, chronic congestive heart failure, or decreased myocardial reserve will have a more profound fall in ventricular function and systolic blood pressure than those with a normal myocardium. This negative inotropic action of contrast material occurs earlier and more profoundly after aortic root or coronary artery injections; after ventriculography the effect occurs about 13 to 16 beats after the injection.[77]

When hyperosmolar contrast material reaches the peripheral circulation, there is vasodilation in response to the rise in serum osmolality[85]; this results in a reduced afterload faced by the ventricle producing an increase in stroke volume and ejection fraction, which in turn causes a temporary decrease in end diastolic volume that is soon restored and even increased by the expansion of circulating blood volume and hemodilution caused by hyperosmolar contrast. The hypotensive effect after ventriculography lasts for 15 to 30 sec; with an increase in venous return there is an increase in cardiac output and systolic blood pressure and a rise in end diastolic volume and pressure, which in normal hearts is accompanied by an increase in dP/dT. There may also be some peripheral sympathetic stimulation due to the acute vasodilation, which promotes an increase in myocardial contractility and cardiac output. The hemodynamics return to base-line values after 5 to 15 min, depending upon the amount of the injection and the number of previous injections. The effects of contrast injections are cumulative and are more pronounced in patients with poor myocardial function, hypotension, and a low serum calcium. The effects are attenuated by the use of lower-osmolality agents[86] and nonionic contrast material[87] and by the addition of calcium to the contrast material[88] or administered intravenously before contrast injection. These effects are particularly important in neonates, infants, and patients who have been taking diuretics chronically, who may have a low serum calcium.[89,90] The administration of furosemide before angiography hastens the elimination of iodine and sodium from the circulation and shortens the duration of the cardiovascular effects.[91]

Injection of contrast material into the pulmonary circulation causes an abrupt rise in pulmonary artery, right ventricular, and right atrial pressures during the first five beats after the injection due to the speed and volume of the injection.[92] Injection of a large volume of contrast into the main pulmonary artery in patients with pulmonary hypertension may produce a stretch reflex vasoconstriction,[93] which may be particularly disastrous in patients with Eisenmenger's syndrome or primary pulmonary hypertension. However, the major effect of hyperosmolar contrast injection into the pulmonary arteries is that of vasodilation and a reduction in pulmonary vascular resistance; any persistent rise in pulmonary artery pressure is due to an increase in cardiac output and pulmonary blood flow. Patients with elevated pulmonary resistance will have a greater increase in pulmonary artery pressure due to the reduced compliance of the pulmonary vascular bed.

Toxic Reactions

Allergic reactions are rare without a previous exposure to contrast agents, especially in the pediatric population.[74] If there has been a history of previous allergy, reactions can be minimized by the administration of an antihistamine before angiography. Renal damage has been reported after angiography and probably results from hyperosmolar tubular damage with resulting hematuria and proteinuria with casts.

It has been recommended that the dose of contrast material not exceed 4 mL/kg in infants and children. However, careful timing of injections, administration of fluid and diuretics, and supplemental calcium doses will reduce the toxicity and cumulative hemodynamic effects, allowing up to 6 mL/kg of contrast material to be given over a period of 2 to 3 hr.

DOSE OF CONTRAST MATERIAL

To visualize anatomic detail in a normal-sized ventricle optimally, my colleagues and I use 1.0 to 1.25 mL/kg of contrast material injected at a rate of 0.5 to 1.0 mL/kg/sec. For smaller ventricles, such as a hypertrophied right ventricle in a patient with tetralogy of Fallot, we use a lesser dose of 1.0 mL/kg at an injection rate of 1.0 mL/kg/sec. This same dose is used to opacify normal pulmonary arteries and the ascending aorta. A slightly smaller dose of 0.7 to 0.8 mL/kg is used in the descending thoracic aorta.

For a dilated ventricle with large flow, such as the left ventricle with a large left-to-right shunt, a dose of 1.5 to 2.0 mL/kg at a flow rate of 1.0 to 3.0 mL/kg/sec is used. For example, in an infant with truncus arteriosus and a heart rate of 150 beats/min, a volume of 2.0 mL/kg at flow rate of 3.0 mL/kg/sec will be needed to opacify the truncus and pulmonary arteries adequately. When studying ventricular function, a slower rate of injection over three to five cardiac cycles will reduce the incidence of premature

ventricular contractions and allow several cardiac cycles to be studied for ventricular volume and wall-motion analysis. For slow injections, a slightly larger amount of contrast material is used than that for a normal-sized ventricle.

As a general principle, the shortest, widest catheter with multiple side holes should be used for ventriculography. The rate of contrast delivery into the chamber varies inversely with the viscosity of the contrast material, the catheter length, and directly with the lumen diameter. When long, small-lumen catheters are used, high-pressure injections will cause straightening of the catheter, which may recoil into the proximal chamber or against the ventricular wall and cause staining of the myocardium. The more curved the catheter inside the heart, the greater the rise time should be for the injection.

ANGIOGRAPHIC DEMONSTRATION OF CARDIOVASCULAR ANATOMY

Angiographic definition of cardiovascular anatomy should show the morphology, position, relations, connections, and function of the cardiac chambers, valves, and vessels entering and leaving the heart. Consideration must be given to the spatial orientation of a particular structure and whether it is best seen en face or in profile to a particular image intensifier.

Biplane video fluoroscopy and cineangiography are essential in pediatric cardiac catheterization laboratories. Because of the greater exposition of intracardiac anatomy obtained by angled angiographic views, various configurations of C or U arms carrying the x-ray tubes and image intensifier are employed to obtain biplane, angled projections of specific areas of the heart.

Radiologic Nomenclature

The direction of the x-ray beam determines the order of names when describing a particular x-ray projection. For example, if the x-ray tube is below the examination table and the image intensifier directly above the patient, the projection is called posteroanterior (PA) (Fig. 55–1).

When the image intensifier is tilted sagittally toward the patient's head, the x-ray beam travels caudocranially (Fig. 55–2); this is often called cranial angulation. When the image intensifier is tilted toward the patient's feet, the x-ray beam travels in a craniocaudal direction, but is often referred to as caudal angulation.

When the image intensifier is tilted to the right or left of the

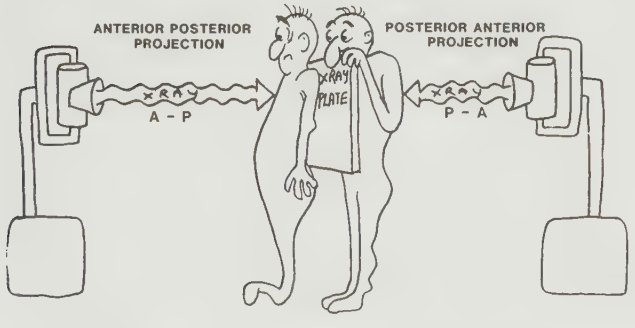

Fig. 55–1. Nomenclature of x-ray projections. The direction of the x-rays from the x-ray tube to the image intensifier or x-ray film determines the order of the names.

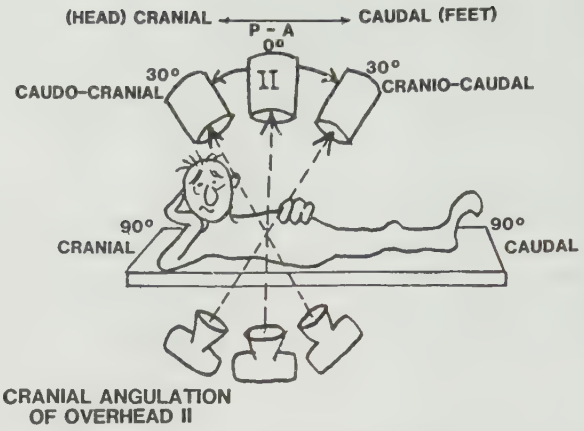

Fig. 55–2. Nomenclature of x-ray projections–sagittal angulation. Cranial angulation of the overhead image intensifier (I.I.) causes the x-ray to travel in a caudocranial direction.

patient, the part of the body nearest the image intensifier determines the name. For example, if the lateral image intensifier is to the left side of the patient, the projection is called left lateral; when the vertical image intensifier is tilted 30 degrees toward the patient's left, the view is called left anterior oblique (LAO) (Fig. 55–3A and 55–3B). If the image intensifier is below the horizontal plane on the left side, the position is left posterior oblique (LPO).

Standard x-ray projections for angiocardiography have usually been in the PA and lateral projections; some early experiments with angled angiography in the 1950s were unsatisfactory because of distortion produced by the x-ray equipment.[94] However, further experiments revealed that tilted or angled angiography (later known as "axial angiography") produced much more information than the standard views.[95,96] While certain congenital cardiac malformations have a constant number and form of defects, the variation in morphology, position, and a degree of deformity varies considerably among individual patients. The angiographer must have a thorough knowledge of normal and abnormal cardiac anatomy; with precatheterization echocardiography and the information obtained from the catheter course through the heart, one should be able to "previsualize" the internal anatomy of a given heart before angiography. The x-ray tubes and/or the patient are positioned to visualize specific parts of the intracardiac anatomy optimally. Several injections will be required to image all of the defects completely in a particular heart and more than one injection may be required to image one particular anomaly completely.

Being mindful of the constraints of the amount of contrast material that can be given to a particular patient, the first injection is made in the chamber or vessel that provides the most information for the immediate medical or surgical management of that patient, in case this is the only injection that can be performed.

Many anomalies in a heart with multiple defects can be well visualized by echocardiography or other noninvasive means; angiocardiography should be confined to lesions or defects that have not been previously clearly defined.

Common X-Ray Projections

Different manufacturers of x-ray equipment have their own systems and nomenclature for the positions of the image intensifiers and x-ray tubes. Some laboratories have fixed PA and lateral tubes;

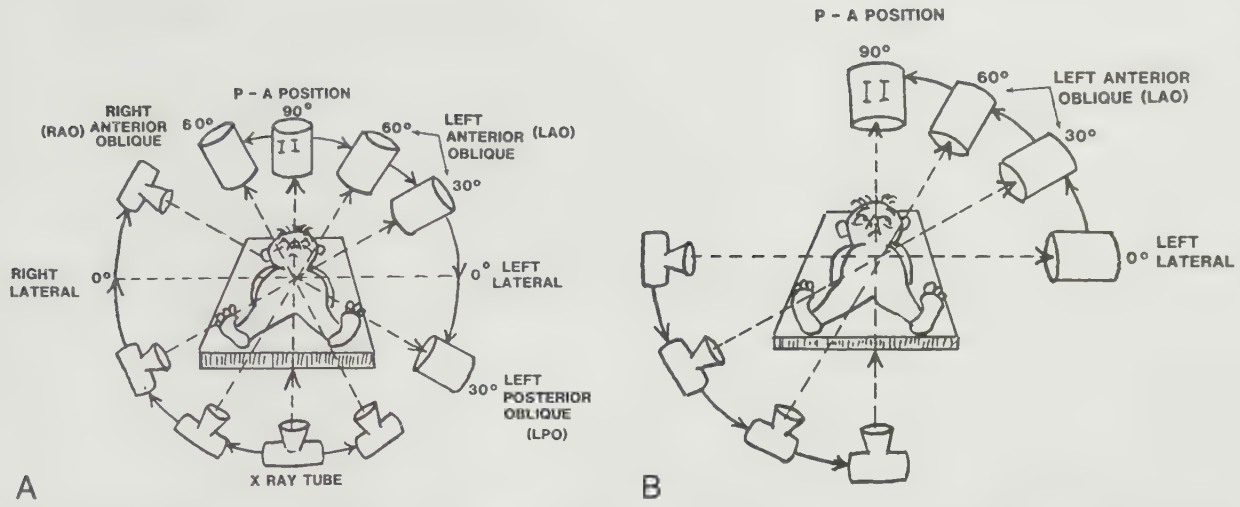

Fig. 55–3. Axial angiography nomenclature: The part of the body nearest the image intensifier determines the name of the projection (see text). (A) Positions of the vertical image intensifier. (B) Positions of the horizontal image intensifier.

to obtain axial views of the heart, one has to move the patient. Other systems have either C arms or U arms, which allow motion of the tubes and intensifiers around three axes.

By convention, the position of the vertical PA image intensifier, when positioned directly above the patient, is considered to be at 0 degrees, while the orthogonally positioned horizontal or lateral image intensifier is at 90 degrees. This convention may vary among laboratories, some designating the lateral tube to be at 0 degrees and the PA tube to be at 90 degrees (Table 55–4).

When imaging congenital heart defects, the principles of axial angiography are 1) place the long axis of the heart perpendicular to an x-ray beam (Fig. 55–4) and 2) rotate the heart or x-ray beam so as to profile the areas of the heart that are to be imaged (Fig. 55–5) (Table 55–5).

Standard Projections

Posteroanterior and Lateral Views

The vertical image intensifier is at 0 degrees directly above the patient, while the horizontal intensifier is at 90 degrees on the left side of the patient.

Right Anterior Oblique (RAO) and Left Anterior Oblique (LAO) Projections

Moveable X-Ray Tubes and Intensifiers. The vertical image intensifier is tilted 30 to 45 degrees toward the patient's right (RAO projection) and the horizontal image intensifier is elevated 30 to 45 degrees from the horizontal position (LAO projection). The x-ray tube-intensifier axes do not have to be orthogonal and each

Table 55–4. X-Ray Projections

	Image Intensifier Position	
Common Views	*Vertical*	*Horizontal*
PA and lateral	90° PA	0° LAT
RAO, LAO	30–60°	30–60° LAO
Long axial	30–60° RAO	30–45° LAO + 30–45° Caudocranial
Four chamber	60° LAO 20–30° Caudocranial or 30–40° RAO	0° Lateral or 30° LAO 60° LAO + 20–30° Caudocranial
Sitting up view "cranial"	30–40° Caudocranial	0° Lateral
Aortic orifice "down-the-barrel"	90° PA	10–20° LPO + 20–30° Craniocaudal
Left ventricular "down-the-barrel"	90° PA	20° LPO + 30° Craniocaudal
Aortic orifice in TGA "down-the-barrel" with balloon occlusion of ascending aorta	45–60° Craniocaudal +0–20° LAO	0° Lateral

RAO = right anterior oblique; LAO = left anterior oblique; TGA = transposition of the great arteries; LPO = left posterior oblique.

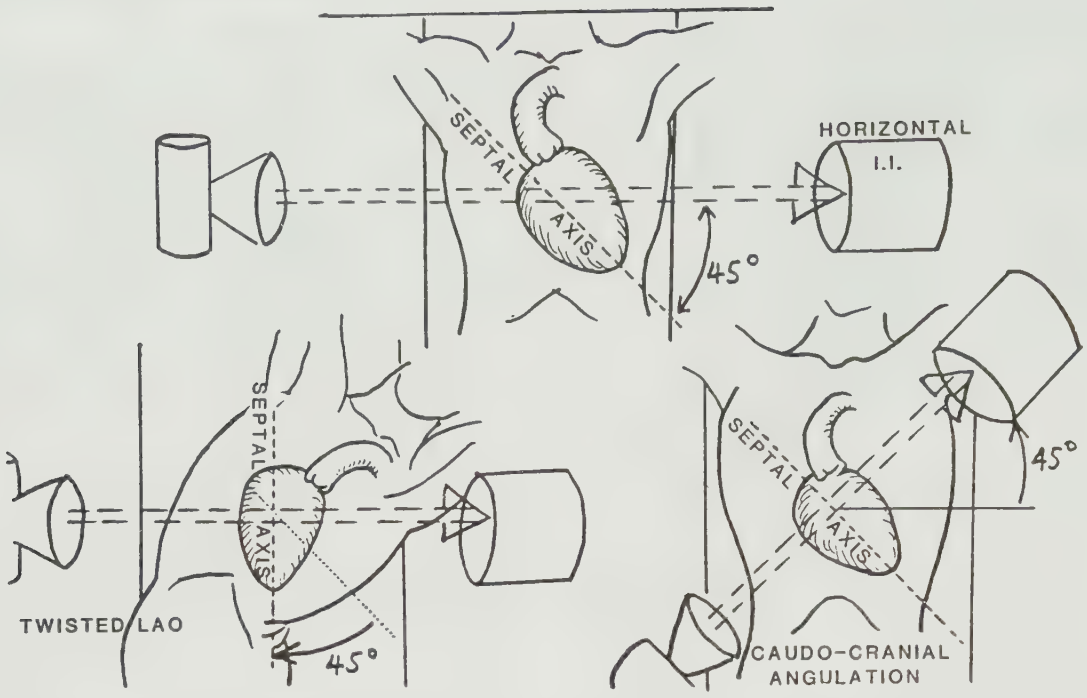

Fig. 55–4. Axial angiography. Aligning the long axis of the heart (septum) perpendicular to the horizontal image intensifier.

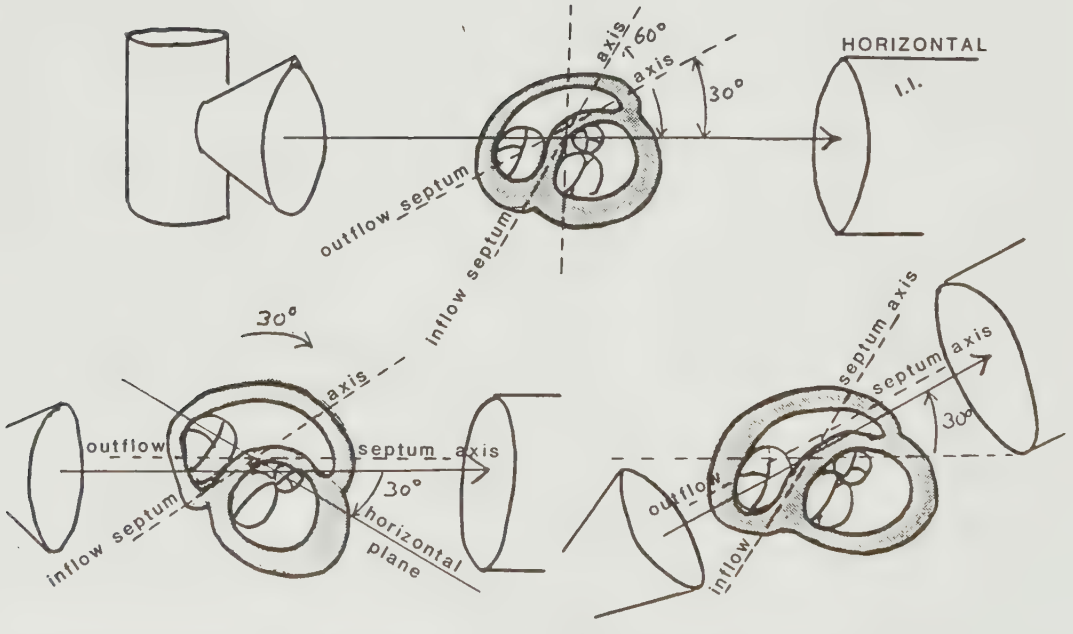

Fig. 55–5. Axial angiography. Profiling the outflow septum of the left ventricle with the horizontal image intensifier.

Table 55–5. Angiographic Views for Congenital Heart Defects

Diagnosis	*Injection Site*	*Vertical Image Intensifier*	*Displays*	*Horizontal Image Intensifier*	*Displays*
Ventricular septal defect	Left ventricle	Right anterior oblique	Ventricular septal defect: supracristal outlet trabecular Mitral regurgitation prolapse Aortic valve Left ventricular function	Long axial	Ventricular septal defect: perimembranous Inlet muscular Trabecular Mitral prolapse Aortic valve Coarctation
	Left ventricle	4-Chamber	Ventricular septal defect: canal type trabecular septum Atrioventricular valves: leaflets straddling	Lateral	Ventricular septal defect: supracristal Mitral regurgitation Patent ductus arteriosus Coarctation
	Right ventricle	Posteroanterior	Ventricular septal defect negative hole	Lateral	Ventricular septal defect: supracristal
Atrioventricular canal	Left ventricle	Posteroanterior	"Gooseneck" Subaortic stenosis Left-ventricular-to-right-atrium shunt	Lateral	Mitral regurgitation Patent ductus arteriosus Coarctation
	Left ventricle	Long axial	Ventricular septal defect: outflow septum trabecular septum Left ventricular outflow tract obstruction Coarctation Anterior bridging leaflet	Right anterior oblique	Mitral regurgitation Septal leaflet commissure Mural leaflet Left ventricular function
	Left ventricle	4-Chamber	Ventricular septal defect: inlet subvalvular inlet muscular Atrioventricular valve attachment Left-ventricle-to-right-atrium shunt	Long axial	Ventricular septal defect: outflow septum Trabecular Left ventricular outflow tract obstruction Coarctation Anterior bridging leaflet
Atrial septal defect	RUPV	4-Chamber	Atrial septal defect: secundum primum superior sinus venosus inferior sinus venosus	Lateral	Atrial septal defect: primum superior sinus venosus inferior sinus venosus
	Main pulmonary artery	Cranial	Recirculation: Pulmonary vein connection Pulmonary stenosis Pulmonary branch stenosis Cor triatriatum	Lateral	Pulmonary stenosis Left pulmonary artery stenosis Cor triatriatum
	Left ventricle	Right anterior oblique	Mitral valve prolapse	Long axial	Ventricular septal defect Mitral valve prolapse
Patent ductus arteriosus	Patent ductus arteriosus	Cranial	Pulmonary branch stenosis	Lateral	Patent ductus arteriosus
	Descending aorta	Posteroanterior	Coarctation (± balloon occlusion)	Lateral	Patent ductus arteriosus Coarctation
Aortic stenosis	Left ventricle	Right anterior oblique	Aortic stenosis: valve subvalve supravalve	Long axial	Left ventricular outflow tract obstruction Ventricular septal defect Coarctation
	Aortic root	Posteroanterior	Aortic stenosis: valve supravalve regurgitation	Orifice view	Annulus Cusps Orifice

Table 55–5. Angiographic Views for Congenital Heart Defects *Continued*

Diagnosis	*Injection Site*	*Vertical Image Intensifier*	*Displays*	*Horizontal Image Intensifier*	*Displays*
Pulmonary stenosis	Right ventricle	Cranial	Right ventricle muscle bundle Infundibulum Annulus Valve Main pulmonary artery Pulmonary branch stenosis	Lateral	Right ventricle muscle bundle Infundibulum Annulus Valve Main pulmonary artery Left pulmonary artery stenosis
	Main pulmonary artery	Caudal	Annulus Cusps Orifice	Lateral	Annulus Valve Main pulmonary artery
Total anomalous pulmonary venous return	Main pulmonary artery	Posteroanterior	Pulmonary venous return	Lateral	Pulmonary venous return
	Pulmonary veins	Posteroanterior	Pulmonary venous connection	Lateral	Pulmonary venous connection
	Posteroanterior wedge	Posteroanterior	For mixed return	Lateral	For mixed return
Coarctation	Left ventricle	Right anterior oblique	Left ventricular outflow tract Muscular ventricular septal defect	Long axial	Left ventricular outflow tract Ventricular septal defect Coarctation
	Aortic root	Posteroanterior	Aortic stenosis Arch vessels Collaterals Vascular ring Coarctation	Lateral	Coarctation Patent ductus arteriosus
Tetralogy of Fallot	Right ventricle	Cranial	Infundibulum Valve Main pulmonary artery Pulmonary branch stenosis	Lateral	Infundibulum Valve Main pulmonary artery Left pulmonary artery Ventricular septal defect
	Right ventricle	Right anterior oblique	Right ventricular outflow tract Valve	Long axial	Ventricular septal defect Aortic override
	Left ventricle	Right anterior oblique	Left ventricle size	Shallow Long axial	Ventricular septal defect: perimembranous Muscular Aortic override Double-outlet right ventricle Left ventricular outflow tract
	Aortic	Right anterior oblique	Coronary arteries: right main	Long axial	Origin of: right coronary artery Left coronary artery Left anterior descending coronary artery
Pulmonary artery atresia, ventricular septal defect	Right ventricular outflow tract	Cranial	Infundibulum	Lateral	Infundibulum
	Aortic root	Posteroanterior	Coronary arteries Proximal collateral arteries Shunts	Long axial Patent ductus arteriosus	Coronary arteries
	Descending aorta	Posteroanterior	Collaterals	Lateral	Collateral arteries

Table 55–5. Angiographic Views for Congenital Heart Defects *Continued*

Diagnosis	*Injection Site*	*Vertical Image Intensifier*	*Displays*	*Horizontal Image Intensifier*	*Displays*
Pulmonary artery atresia, ventricular septal defect *(Continued)*	Descending aorta	Cranial	Collateral arteries Pulmonary confluence	Lateral Main pulmonary artery	Pulmonary confluence
	Selective collaterals	Posteroanterior	Pulmonary confluence Segmental blood supply	Lateral Segmental blood supply	Pulmonary confluence
	Vein wedge	Posteroanterior	Pulmonary confluence	Lateral	Main pulmonary artery
Pulmonary valve atresia	Right ventricular outflow tract	Cranial	Infundibulum Right ventricle size, components Sinusoids	Lateral	Infundibulum Right ventricle size, components
	Descending aorta	Posteroanterior	Patent ductus arteriosus Pulmonary arteries	Lateral	Patent ductus arteriosus Main pulmonary artery
	Right ventricular outflow tract + descending aorta	Posteroanterior	Main pulmonary artery-right ventricular outflow tract continuity	Lateral	Main pulmonary artery-right ventricular outflow tract continuity
	Right atrium	4-Chamber	Atrial septal defect	Lateral	Atrial septal defect
Tricuspid atresia	Left ventricle	Right anterior oblique	Mitral regurgitation Left ventricle function	Long axial	Ventricular septal defect
	Right ventricle	Cranial	Right ventricle size Right ventricular outflow tract Pulmonary arteries	Lateral	Ventricular septal defect Right ventricular outflow tract
	Main pulmonary artery	Cranial	Pulmonary arteries Pulmonary branch stenosis	Lateral	Pulmonary stenosis
	Right atrium	4-Chamber	Atrial septal defect Right atrial appendage	Lateral	Atrial septal defect Right atrial appendage
Transposition of the great arteries	Left ventricle	Right anterior oblique	Left ventricular outflow tract Right pulmonary artery	Long axial	Left ventricular outflow tract Ventricular septal defect Left pulmonary artery
	Right ventricle	Posteroanterior	Tricuspid regurgitation Right ventricle function, size	Lateral	Ventricular septal defect Patent ductus arteriosus Coarctation
	RUPV	4-Chamber	Atrial septal defect	Lateral	Atrial septal defect
	Aortic root	Caudal	Coronary artery origin, course	Lateral	Coronary artery origin, course Aortic valve Coarctation Patent ductus arteriosus
Postoperative Senning/Mustard	Left ventricle	4-Chamber	Left ventricular outflow tract Pulmonary venous return	Long axial Pulmonary venous return	Left ventricular outflow tract
	Right ventricle	Right anterior oblique	Right ventricle function	Lateral	Right ventricular outflow tract Ventricular septal defect
			Tricuspid regurgitation	Tricuspid regurgitation	
Postoperative arterial switch	Left ventricle	Right anterior oblique	Left ventricle function Ascending aortic stenosis	Long axial Ascending aortic stenosis	Left ventricular outflow tract Ventricular septal defect
	Right ventricle	Cranial	Main pulmonary artery stenosis	Lateral	Main pulmonary artery stenosis
	Aortic	Posteroanterior	Coronary artery stenosis	Long axial	Coronary artery stenosis

Table 55–5. Angiographic Views for Congenital Heart Defects *Continued*

Diagnosis	*Injection Site*	*Vertical Image Intensifier*	*Displays*	*Horizontal Image Intensifier*	*Displays*
Truncus arteriosus	Left ventricle	Right anterior oblique Truncal valve	Left ventricle size Right pulmonary artery	Long axial Left pulmonary artery	Ventricular septal defect Truncal valve
	Truncus	Cranial	Truncal valve Main pulmonary artery Right pulmonary artery Left pulmonary artery	Left anterior oblique	Truncal valve Main pulmonary artery Left pulmonary artery
	Right ventricle	Posteroanterior	Right ventricular outflow tract Truncus	Lateral	Truncus Right ventricular outflow tract
Ebstein's	Left ventricle	Right anterior oblique	Left ventricle function Mitral prolapse	Long axial	Ventricular septal defect Left ventricular outflow tract
	Right ventricle	Cranial	Right ventricle size, function Right ventricular outflow tract Pulmonary valve Tricuspid regurgitation stenosis	Lateral	Right ventricular outflow tract Pulmonary valve Tricuspid regurgitation
	Atrialized Right ventricle	Posteroanterior	Chamber size Tricuspid stenosis Annular regurgitation	Lateral	Chamber size Annular regurgitation Atrial septal defect
Single ventricle	Main chamber	Posteroanterior	Ventricle morphology Small chamber: position morphology Ventricular-Arterial: connections relations Pulmonary outflow tract Pulmonary branches Pulmonary venous return	Lateral	Ventricle morphology Small left ventricle posterior Arterial morphology Arterial relations Ventricular septal defect
	Main chamber	Right anterior oblique	Ventricular septal defect Anterior-left right ventricle Atrioventricular valve regurgitation Main pulmonary artery Right pulmonary artery	Lateral	Ascending aorta Left pulmonary artery Ventricular septal defect
	Left atrium	4-Chamber	Atrioventricular valve: morphology connections straddling	Lateral	Ebstein's anomaly of left atrioventricular valve

intensifier may be tilted to different positions to display best the diagnostic information available from its aspect of the heart.

Fixed X-Ray Tubes. The patient's right shoulder is elevated 30 to 45 degrees from the table top and rested on a foam wedge. This presents the RAO projection to the vertical image intensifier and the LAO projection to the lateral intensifier.

Long Axial Projection (Tilted Left Anterior Oblique)

In one view, after positioning the image intensifiers in the RAO and LAO positions, the horizontal image intensifier is tilted 20 to 30 degrees toward the patient's head (cranial) so that the horizontal x-ray beam is perpendicular to the elongated long axis of the heart. The LAO elevation places the left ventricular outflow tract and septum in profile to the x-ray beam. The long axial projection has been used for right ventricular injections but the trabecular septum wraps around the left ventricle and the septal profile is not as sharp as that seen from a left ventricular injection. The vertical image intensifier can be tilted caudally 20 to 30 degrees to produce an elongated right anterior oblique projection.

In another view, the patient is twisted from the hips toward the horizontal image intensifier to align the long axis of the heart parallel to the table and perpendicular to the horizontal x-ray beam.

The right shoulder is then elevated 30 degrees to profile the left ventricular outflow tract and septum to the horizontal x-ray beam.

Four-Chamber View (Hepatoclavicular)

This projection is used to look at the crux of the heart with both atria and ventricles en face to the image intensifier with the atrioventricular valves in profile. Either the vertical or horizontal image intensifiers can be used for this projection.

In one view, the vertical image intensifier is tilted 30 degrees LAO and 20 to 30 degrees cranial. The horizontal tube can remain in the left lateral position. Alternatively, the horizontal intensifier can be elevated 60 degrees LAO from the horizontal position and then tilted 20 to 30 degrees cranially. The vertical image intensifier can be rotated 30 to 45 degrees RAO with or without a caudal tilt of 20 to 30 degrees to show an elongated RAO view of the left ventricle.

In another view, the patient's chest is elevated 30 degrees from the table top using a foam wedge; the right shoulder is elevated 20 to 30 degrees to present a four-chamber view to the vertical image intensifier and a long axial view to the horizontal image intensifier.

Cranial Angulation (Sitting-up View)

In one view, the vertical image intensifier is rotated 30 degrees in a cranial direction (caudocranial x-ray projection) and the patient's head rotated to one side. This elongates the right ventricular outflow tract, main pulmonary artery, and bifurcation. When the main pulmonary artery is dilated, the origin of right and left branches may not be well seen from this straight cranial angulation. Therefore one should use cranial angulation of both the vertical and horizontal image intensifiers in a 30-degree RAO and LAO projection to see the origin of the right and left pulmonary arteries.

In another view, the patient's chest is raised 30 degrees from the table top and the head allowed to drop back over the foam wedge. The horizontal intensifier is moved to obtain a left lateral projection.

Aortic Orifice View

With normal origin of the aorta from the left ventricle, the horizontal intensifier is lowered 10 to 15 degrees left posterior oblique (LPO) and tilted caudally 10 to 30 degrees.[97] The position of the horizontal image intensifier will depend upon the orientation of the aortic annulus, which may be almost vertical in some patients and almost horizontal in others.

The patient may also be twisted to the right from the hips with the left shoulder elevated 10 to 15 degrees so that the aortic orifice faces the horizontal image intensifier. The injection is made as close as possible to the aortic valve to fill both coronary arteries without producing aortic regurgitation. This projection outlines the sinuses of Valsalva, the aortic annulus, and valve cusps and has been used to look at the origin of the coronary arteries and the morphology of the aortic valve, and to measure aortic valve area.

Right Ventricular Outflow Tract (Orifice) View

This is useful for looking at the pulmonary annulus while injecting in the main pulmonary artery or the aortic annulus in transposition of the great arteries. The vertical image intensifier is tilted 30 to 45 degrees in a caudal direction with a variable degree of LAO rotation depending upon the sagittal orientation of the main pulmonary artery or ascending aorta. The origin of the coronary arteries is well seen in transposition of the great arteries and the morphology of the pulmonary valve in pulmonary stenosis.

Pulmonary Artery Wedge Angiography

In order to evaluate the morphology of the peripheral pulmonary circulation in the primary pulmonary lobule, pulmonary arterial wedge angiograms are taken in a high magnification mode to assess the lobar architecture and microcirculation in the primary pulmonary lobule; the morphology of the muscular pulmonary arteries and supernumerary arteries; the background blush that constitutes the arterioles, capillaries, and venules; communications between pulmonary arteries and veins; and the pulmonary venous return.[98]

Low kilovoltage and high milliamperage are used to maximize contrast for sharp edge definition of the small pulmonary arteries. A focal spot of 0.3 to 0.6 mm is used and a film rate of 30 frames per second with an exposure of 4 msec. An end-hole catheter is wedged into a distal pulmonary artery in the periphery of the lung, preferably at the costophrenic angle or chest wall. A small test injection of 0.2 to 0.5 mL is made to evaluate the alignment of the pulmonary lobule with the vertical image intensifier. If there is foreshortening of the central pulmonary artery in the PA projection the lateral projection or biplane filming should be used. The image intensifier is raised as high as possible from the table top to increase magnification without loss of edge definition. The field is then adjusted to visualize the peripheral arterial tree as well as the venous return to the left atrial border. One should try to center the x-ray field over tissue of uniform density such as the lung without any liver or heart shadow present.

A very slow hand injection of 0.5 to 1.0 mL of contrast material is made to outline the central pulmonary artery and small branches. As soon as the vein starts to fill, the catheter is flushed with 2 to 5 mL of flush solution to wash the contrast material through the lobule and visualize the capillary background blush and venous return.

If it is not possible to wedge an end-hole catheter into the peripheral pulmonary arteries, an end-hole balloon catheter can be inflated in a sublobar artery and 1 to 5 mL of contrast can be injected to fill the peripheral pulmonary arteries. The balloon is then deflated and the pulmonary blood flow will wash out the contrast into the capillaries and pulmonary veins. If the injection is made too proximally, too many vessels will be filled and will obscure the terminal branches and supernumerary vessels and not enough contrast will be available to opacify the smaller pulmonary lobules.

Wedge angiography can identify morphologic patterns associated with high pulmonary blood flow with low resistance, high pulmonary blood flow with elevated pulmonary artery pressure, and elevated pulmonary resistance and obstructed pulmonary vascular disease (Heath and Edwards Grade IV). Anomalies of pulmonary venous connection can also be demonstrated with very small amounts of contrast. Pulmonary venous varices and pulmonary venous obstruction can be identified more readily by this technique than by main pulmonary artery injections.

Pulmonary Venous Wedge Angiography

When an injection is made into an end-hole catheter wedged in a pulmonary vein, there is retrograde filling of the pulmonary

arteries if the pulmonary artery pressure is low or the blood flow in the pulmonary arteries is less than normal.[99] This technique is used in patients with pulmonary atresia to visualize the central pulmonary arteries and the connections of the lobar blood supply when there are several systemic collateral vessels.

An end-hole catheter is wedged into a pulmonary vein and a very slow hand injection of 0.3 to 0.6 mL/kg is made at a rate of 0.5 mL/sec. This amount of contrast will load several pulmonary lobules with contrast material. The catheter is then flushed by hand injection with 5 to 10 mL of flush solution at a flow rate of 1.0 mL/sec.

The fields are set to visualize the tip of the catheter and, more importantly, the hilar and mediastinal regions. The filming rate is 30 frames/sec to allow for the slow injection through the capillary bed and retrograde flow to the proximal pulmonary arteries. If more than one blood vessel supplies the lung, several injections may have to be made to define the small central pulmonary arteries and confluence. Injection into a lobe supplied by a systemic collateral vessel may result in washout of the contrast and no central filling of the collateral or true pulmonary artery confluence.

Pulmonary venous wedge angiograms are never performed with a power injector because the force of the injection will extravasate contrast material into the lung parenchyma and bronchi.[100] Coughing during an injection is quite common but no serious complications or hemoptysis have occurred in over 300 studies.

An alternative technique is to inflate an end-hole balloon catheter in a more proximal pulmonary vein and inject a larger amount of contrast material into several peripheral pulmonary veins. This contrast is then flushed with a larger amount of flush solution to fill the pulmonary arteries in retrograde fashion.

Aortic Occlusion Angiography

Injections of contrast in the ascending or descending aorta may not provide good visualization of small aortic branches such as the coronary arteries or systemic collateral vessels because of the fast runoff down the aorta. Using an angiographic balloon catheter with side holes proximal to the inflated balloon, one can inflate the balloon just distal to the point of interest.[101,102] A power injection is then made, forcing the contrast to fill the proximal aorta and small side branches. The balloon is then deflated quickly after the injection. With the balloon inflated just proximal to the brachiocephalic arteries, an injection in the proximal ascending aorta will visualize the coronary arteries in transposition of the great arteries, especially when the vertical intensifier is tilted caudally (see above). Angiography with balloon occlusion of the descending aorta just above the diaphragm will provide excellent visualization of systemic collateral vessels arising from the descending aorta in pulmonary artery atresia. When a catheter is passed through a patent ductus arteriosus and a balloon inflated just distal to the ductus, contrast injection will show the ductus as well as the aortic isthmus and coarctation and often the ascending aorta.[103]

HEMOSTASIS AND ANTICOAGULANTS

Precatheterization clotting studies are drawn on all newborns and patients with a hematocrit over 60%; some newborns require the administration of vitamin K before catheterization. Some patients may have disorders of blood clotting or platelets due to infection or shock; fresh frozen plasma and fresh platelets should be administered if clotting disorders are identified. One unit of fresh packed red cells, or at least 20 mL/kg, should also be available during all catheterizations of infants of less than 5 kg because of the relatively large blood loss when exchanging catheters or sheaths in infants as compared with other children.

The use of hemostasis or bleed-back valves on percutaneous sheaths will minimize blood loss during catheter exchanges or when there is poor size tolerance between the catheter and sheath size. When using a small catheter in a larger sheath, back flow of blood into the sheath around the catheter may result in thrombosis inside the sheath; this clot could be flushed into the circulation during catheter exchanges or flushing of the side arm of the hemostasis valve. In my laboratory we have used a constant slow infusion of heparinized saline through a bleed-back valve in patients who have required prolonged catheter manipulation.

If a femoral or saphenous cutdown is performed, the distal vessel is ligated or secured with a heavy ligature if later repair is planned. A temporary hemostasis suture is placed around the proximal part of the common femoral vein while the catheter is in the heart. This prevents back bleeding during the catheterization and also helps in repairing the vein after the catheterization.

Anticoagulants are not routinely used during a venous catheterization. If a retrograde arterial catheterization is likely to take longer than 30 min systemic heparinization at 50 U/kg should be instituted. Patients with marked polycythemia may have accelerated clotting and a consumptive coagulopathy if the hematocrit is over 60%[104,105]; phlebotomy with plasma replacement will reduce this tendency.

POLYCYTHEMIA AND ANEMIA

Patients who are markedly polycythemic have a marked elevation of blood viscosity when the hematocrit is above 65%. If the precatheterization hemoglobin is above 20 g/dL, a centrifuged hematocrit is obtained using venous blood to measure the true packed cell volume. An oxygen-carrying capacity of 17 to 19 mL of oxygen/100 mL of blood is desirable (assuming 95% saturation in a normal patient with 10 to 15 g of hemoglobin). If the hematocrit is 65% or greater, we recommend erythropheresis before angiography to reduce the centrifuged hematocrit to 60%.[106] The amount of blood withdrawn is replaced with fresh plasma or 5% albumin solution, which has the same osmolality as plasma. Patients with secondary polycythemia have an elevated blood volume on the order of 90 to 110 mL/kg (average, 100) due to the increased red cell mass.[107]

$$\text{Blood volume to withdraw} = \text{wt (kg)} \times 100 \times \frac{\text{observed hematocrit} - \text{desired hematocrit}}{\text{observed hematocrit}}$$

A similar calculation can be used to increase the patient's oxygen-carrying capacity if there is systemic hypoxemia and low oxygen-carrying capacity.

Reduction of the oxygen-carrying capacity and blood viscosity is performed cautiously in patients with obstruction to pulmonary blood flow, such as tetralogy of Fallot, or those with high pulmonary resistance. A reduction in blood viscosity will result in a greater fall in systemic resistance than in pulmonary resistance, which may induce more right-to-left shunting and systemic hypoxemia. On the other hand, patients with transposition physiology

tend to improve their systemic saturation with a reduction in hematocrit to 60%.[106]

DRUGS

Intravenous drug infusions are maintained on arrival at the catheterization laboratory. Once monitoring catheters have been inserted, the infusion rate of these drugs may be changed and the effects recorded. Maintenance fluid in infants and premature babies is 10% glucose with one-quarter to one-fifth normal saline. Regular checks of the blood glucose are made during the catheterization as the stress of the illness or catheterization may cause hypoglycemia even with 10% glucose administration. Bolus doses of glucose are given intravenously at a concentration of 25%; more-concentrated solutions may cause hypotension due to hyperosmolality.

Half the calculated dose of a drug is administered initially and the effect on the patient observed to make sure that no idiosyncratic or untoward reactions occur. The rest of the calculated dose may then be administered in small aliquots with interval flushing until the desired effect is achieved.

Infants are more susceptible to the central nervous system depressing effects of narcotics and drugs such as ketamine. We have found that a total dose of 0.1 mg of morphine is adequate for sedation in infants under 6 mo of age rather than the usually recommended dose of 0.1 mg/kg.

A bolus intravenous flush of ketamine of 0.5 to 1 mg/kg may result in apnea or extrapyramidal seizures in infants. This dose causes few problems or changes in hemodynamics when infused over 30 to 60 sec.[49]

The dose of lidocaine used for local anesthesia infiltration is carefully monitored, and no more than 5 mg/kg should be given subcutaneously.

Antibiotics are not routinely given before catheterization as the risk of bacterial endocarditis in an otherwise noninfected child is rare after cardiac catheterization. If indicated, cardiac catheterization can be safely carried out in a child who has other signs of sepsis, such as endocarditis, while the usual therapeutic antibiotics are being administered.

If a cutdown is needed for venous access, topical antibiotics can be applied to the wound at closure.

We have found an increased incidence of wound and systemic infections in children who have prostaglandin E_1 infusions for ductal-dependent congenital heart defects. We recommend the routine administration of broad-spectrum antibiotics in all children receiving prostaglandin E_1 and also recommend that the use of this drug be limited to as short a time as possible with as low a dose as possible.

Emergency medications should be drawn up in administration syringes and available during the catheterization. Table 55–6 lists emergency drugs that should be available during a cardiac catheterization and their doses.

COMPLICATIONS OF CARDIAC CATHETERIZATION

The mortality and morbidity associated with cardiac catheterization is directly related to the underlying cardiopulmonary defect and the general condition of the patient rather than to age and size.[108] The moribund, acidotic, hypoxic neonate with poor perfusion, who has not responded to precatheterization medications and management, has a poor chance of survival with or without cardiac catheterization. Such infants are likely to have complex or inoperable cardiopulmonary defects and usually die in spite of, rather than because of, the catheterization.

The incidence of complications and the number of deaths from cardiac catheterization have decreased sharply over the past 20 yr. Cardiac catheterization techniques, vascular access, catheter design and materials, the quality and type of imaging, and the type of contrast materials used for imaging have undergone considerable refinements and have improved the quality and safety of cardiac catheterization and angiography over the past 20 yr. The indications for a cardiac catheterization have also changed with the introduction of other imaging modalities, such as two-dimensional echocardiography.

Mortality

A cooperative study on cardiac catheterization[109] gathered data on the incidence and type of complications that occurred during 12,367 cardiac catheterizations carried out over a 2-year period from 1963 to 1965. There were 4050 children less than 14 yr of age included in this study and 1161 were under 1 year of age. A total of 55 deaths (4%) occurred within 24 hours of the catheterization and 40 of these (72%) were in children. Twenty-nine (72%) of the pediatric deaths were in infants less than 2 months of age, who had a total mortality rate of 6%. The mortality rate for the 2-to-11-months age group was 1.2% and thereafter was 0.3 to 0.05%, comparable to all other age groups, including adults.

Perforation of the heart by a catheter or after angiocardiography occurred in 24 patients less than 15 years of age and resulted in nine deaths in patients aged 4 days to 4 months. Bradycardia and complete heart block was poorly tolerated in infants and resulted in seven deaths in severely ill patients age 36 hours to 6 weeks. Ventricular tachycardia precipitated the death of a 2-month-old infant with mitral atresia, while supraventricular tachycardia preceded the death of a 7-month-old child with congestive cardiomyopathy.

Progressive deterioration and death ensued in eight patients who were critically ill or moribund from severe congestive heart failure, cyanosis, or uncorrectable cardiac defects.

Twelve patients died within 24 hours of the catheterization after being transferred to the ward and it was argued that "after catheterization, critically ill infants should be observed and monitored in an environment resembling an intensive care or coronary care unit."[109]

Of the 55 patients who died, 27 (49%) were in New York Heart Association Class IV, 11 (20%) in Class III, 5 (9%) in Class II, and 1 (1.8%) in Class I. Twenty-three of these deaths occurred during the catheterization, while 19 occurred within 24 hours and 13 died more than 24 hours after the catheterization.

Since that initial collaborative study, many changes have taken place in the methods of catheterization and angiography, medical management, operative techniques, and the type of patients undergoing cardiac catheterization for the investigation of congenital heart disease.

Several later studies of cardiac catheterization complications from the early and late 1970s[108,110,111] showed that the causes of death were similar to those described in the first collaborative study but the incidence was remarkably lower. In all of these later

Table 55–6. Emergency Drugs

Drug	*Intravenous Dose*	*Comment*
Albumin	1.0 g/kg	Volume replacement
Aminophylline	Bolus: 3.0 mg/kg Infusion: 0.7 mg/kg/hr	Hypotension, tachycardia
Atropine	0.01–0.04 mg/kg	Tachycardia, spells in tetralogy of Fallot
Bretylium	5.0 mg/kg, up to 20 mg/kg	
Calcium chloride	50–100 mg/kg	Vagal stimulation
Chloral hydrate	Rectal, by mouth: 25–80 mg/kg	
Chlorpromazine	I.M.: 1.0 mg/kg I.V.: 0.25 mg/kg	Hypotension, hypothermia
Cryoprecipitate	1 unit (bag) = 250 ml FFP	
Dextrose 25%	2.0 ml/kg	
Diazepam	0.10 mg/g	Vasoconstriction in pulmonary hypertension
Digoxin	I.V. digitalizing dose: 20–30 μg/kg	
Diphenhydramine	2.0–5.0 mg/kg	
Dobutamine	1–40 μg/kg/min	
Dopamine	1–30 μg/kg/min Renal dose: 2–5 μg/kg/min	Tachycardia, arrhythmias
Epinephrine 1:10,000	Infusion: 0.10 μg/kg/min Bolus: 0.10 ml/kg	
Fresh plasma	10–15 ml/kg	Hypotension. Ca++ reverses
Furosemide	1–5 mg/kg/dose	
Hydralazine	0.20–1.2 mg/kg	Hypotension
Isoproterenol	0.10 μg/kg/min	Tachycardia, hypotension
Ketamine	0.5–1.0 mg/kg	Apnea, seizures
Lidocaine	Bolus: 1–5 mg/kg Infusion: 20–40 μg/kg/min	Seizures
Mannitol	0.5–1.0 g/kg	
Meperidine HCl	1–2 mg/kg	Hypoventilation
Methoxamine	0.05–0.1 mg/kg	Vasoconstriction
Methylprednisolone	30 mg/kg	
Morphine	0.01–0.1 mg/kg	Hypoventilation, apnoea
Nalorphine	0.1–0.2 mg/kg	
Naloxone	0.01 mg/kg	
Neostigmine	0.025–0.05 mg/kg	
Nitroglycerine	0.1–1.0 μg/kg/mg	Hypotension
Nitroprusside	0.5–10 μg/kg/min	Hypotension, cyanide
Pancuronium	0.1 mg/kg	
Pentothal	10–30 mg/kg	Apnea
Phenobarbital	1–5 mg/kg	Apnea
Phenylephrine	0.01–0.10 mg/kg	Vasoconstriction
Procainamide	10–15 mg/kg over 40 min	Hypotension
Propranolol	0.01–0.025 mg/kg	Bradycardia, hypotension
Succinyl choline	1.0 mg/kg	
Tolazoline	1–2 mg/kg	Hypotension, gastric hyper-acid
Verapamil	0.10 mg/kg	Bradycardia, hypotension

studies, the mortality was highest in infants less than 2 mo of age who were rated as critically ill and had a noncardiac illness or uncorrectable cardiovascular defects. The incidence of deaths related the catheterization procedure itself ranged from 0.26 to 1.6%, and they were due to cardiac perforation, arrhythmias (particularly bradyarrhythmias), and hypotension. Progressive deterioration due to inoperable cardiovascular defects, failed medical treatment, or pulmonary disease with no congenital heart defects resulted in a total pericatheterization mortality rate of 1.6 to 5% in infants less than 12 mo of age.

Patients with the highest mortality were those classified as "critically ill" or "at high risk" and were characterized as being acidemic (PH <7.1), hypoxemic (pO_2 <25 mm Hg), with poor peripheral perfusion and requiring ventilation. These patients comprised 12 to 20% of the infants catheterized, and they had a mortality rate of 30 to 36%. Those considered to be at low risk (30 to 66% of infants catheterized) had a mortality rate of 1.2 to 3.4%.

Stanger et al.[110] studied the complications of cardiac catheterizations in neonates, infants, and children for a 36-mo period from January 1970 to December 1972. There were 218 neonates among this group with 20 deaths (9.2%) within 24 hours of catheterization. Forty-seven patients were severely ill prior to the catheterization with profound hypoxemia (pO_2 less than 25 mm Hg), acidemia (pH less than 7.1) with poor peripheral perfusion or were ventilated during catheterization. Two of these patients died during the catheterization (one with hypoplastic left heart syndrome and one with pulmonary disease) and 15 others died within 24 hours of the catheterization, for a mortality rate of 36.2%. Only two of these patients had remedial cardiac defects. The authors felt that only one patient died as a direct result of the procedure itself and in another patient the relation was not clear.

A similar study of 194 neonates catheterized at less than one week of age was conducted at Texas Children's Hospital between January 1971 and July 1976.[111] There were 10 deaths (5%), 3 (1.6%) of which were related to the catheterization procedure itself, resulting from perforation of the right ventricular outflow tract, right atrium, and umbilical artery. Three patients with pulmonary disease and pulmonary hypertension died within 24 hr of catheterization, and one patient with hypoxic cardiomyopathy died during catheterization. Three patients in critical condition from their congenital heart defects (truncus arteriosus with interrupted arch; coarctation, ventricular septal defect, atrial septal defect, patent ductus arteriosus; ventricular septal defect and atrial septal defect) died within 48 hr of catheterization. Nonfatal complications occurred in 31 patients.

The most recent prospective study was from January to December of 1978 and included 155 neonates less than 28 days of age from the New England Regional Infant Cardiac Program.[108] Thirty-eight of the infants weighed less than 2 kg. Among the neonates, there were 10 deaths within 24 hr of the catheterization and a further nine of the survivors (6.2%) died within 48 hr of the catheterization. Death was attributed to the catheterization in only one patient who had transposition of the great arteries and who died after an embolus lodged in his left anterior descending coronary artery. The other deaths were due to inoperable lesions such as hypoplastic left heart, pulmonary disease, failed medical therapy, or postcatheterization surgical complications. Patients who were judged to be in the high-risk group had 10 times greater mortality than the patients in the low-risk group.

A prospective study performed in the last five years would probably show very few catheterizations of patients with inoperable cardiac lesions and few diagnostic catheterizations of patients with pure pulmonary problems.

However, the major risks of cardiac catheterization are probably the same now as they were in the earlier studies: cardiac perforation and tamponade; blood loss; failure to improve progressive hypoxemia, hypoxia, hypotension, acidemia, or depressed myocardial function; and thrombotic or traumatic occlusion of iliofemoral and brachiocephalic arteries.

Perforation of the heart has become less frequent; this may be due to the use of balloon-tipped catheters. It should be noted that manipulation of these catheters with the balloon deflated is more hazardous since the catheter tip is sharply tapered when the balloon is deflated.

Blood loss represents a more significant problem in neonates and small premature infants than in older infants and children. Blood withdrawal for arterial blood-gas measurement and oxygen saturations for green-dye curves present a cumulative blood loss that may have to be replaced. Using a percutaneous sheath with a bleed-back or hemostasis valve reduces blood loss during catheter exchanges.

Hypotension is common after angiography with ionic contrast material.[76] The degree and incidence of hypotension has been reduced with the introduction of nonionic contrast material in the past few years.[90] Subclinical dehydration may be present in neonates and premature babies because of diuretic administration, nonhumidified respirators, and blood sampling during the catheterization. The first angiogram may produce profound and progressive hypotension and bradycardia in an infant who is barely compensated for preexisting low blood volume. Atrial filling pressures should be checked before angiography; calcium chloride may have to be administered in infants who have had large doses of diuretics prior to the catheterization.

Arterial Complications

Since the introduction of the percutaneous sheath technique, major arterial complications have virtually disappeared.[73,112,113] Minor complications involving decreased femoral or peripheral pulses with pallor and coolness of the limb still occur, but this incidence has also been reduced by systemic heparinization during arterial catheterization.[112] Most of the problems from arterial cannulation improve within 24 hr and rarely does the patient need surgical embolectomy or arterioplasty. Recent reports have shown that the use of streptokinase or urokinase might be helpful in opening up occluded femoral arteries if 24 hr of systemic heparinization does not improve the circulation.[113] Femoral pulses may also be compromised if relatively large catheters are introduced via the umbilical artery. Trauma to the umbilical artery–iliac artery junction may occur or thrombi may accumulate at this junction when the catheter is passed into the descending aorta.

Embolic phenomena are rare and may occur at the same frequency in neonates as in older infants and children. There is a higher risk in children with right-to-left intracardiac shunts or those who are polycythemic. The overall incidence may be as high as 1 to 2%.

Other Complications

Arrhythmias

Transient supraventricular tachycardia, atrial flutter or fibrillation, ventricular tachycardia/fibrillation, and second- and third-degree heart block are the most common major and minor complications occurring during cardiac catheterization. Arrhythmias are usually transient and resolve spontaneously after withdrawal of the catheter stimulation. Fast ventricular rates are usually tolerated well by neonates and infants, except those with tetralogy of Fallot physiology, who become more cyanotic with tachycardia. Bradycardia on the other hand is less well tolerated by infants who rely on increasing heart rate to increase cardiac output. Recent digitalis administration is a risk factor for the development of atrial or ventricular tachycardia as well as third-degree heart block. Catheter manipulation is the usual precipitating cause.

Infections

Systemic infections are rare after cardiac catheterization, and bacterial endocarditis prophylaxis is not recommended in patients undergoing catheterization. Localized wound infections have virtually disappeared since the introduction of the percutaneous sheath technique. I recommend the administration of systemic broad-spectrum antibiotics in children being administered prostaglandin E_1 for as long as this drug is being administered.

SUMMARY

The indications for cardiac catheterization must be assessed in the context of the patient's problems and the information that is necessary to treat these problems. When clear information is not available from one source, other procedures should be used to obtain data pertinent to the clinical situation.

Cardiac catheterization should be used after taking into consideration the patient's problems, available equipment, the skills of the investigating physician and technicians, and the availability of positive therapy.

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CHAPTER 56

Selective Coronary Arteriography in Children with Heart Disease

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Robert J Hall

IMPORTANCE OF SELECTIVE CORONARY ARTERIOGRAPHY IN CHILDREN AND ADOLESCENTS WITH HEART DISEASE

Selective coronary arteriography has been recognized as a major diagnostic tool in cardiology since its advent some three decades ago. In the past 20 years, this technique has found increasing application in pediatric cardiology. Selective coronary arteriography serves as a guide to identification of congenital heart disease[1] and identifies anomalies and disease processes of the coronary arteries in children and young adults. Advances in cardiac surgery and an increase in the incidence of Kawasaki disease are other factors leading to broader application of this diagnostic procedure. Preoperative knowledge of the coronary anatomy serves as a guide to appropriate surgical approach, especially when right ventriculotomy is anticipated. This is particularly important since intraoperative recognition and diagnosis of anomalous coronary arteries can be quite difficult. The presence of pericardial adhesions as a result of previous palliative intrapericardial procedures or intramyocardial course and distribution of a coronary artery makes such a distinction virtually impossible. Even when recognized, an anomalous coronary artery may limit the scope of ventricular incision, thus hindering the surgeon. Major complications with fatal consequences have been reported as a result of inadvertent severing of a vital coronary artery branch.[2]

Aortic root angiography is frequently inadequate in providing accurate diagnosis.[3] This becomes particularly important when the proximal left coronary artery is the focus of interest. Dense opacity caused by contrast material in the aorta and sinuses of Valsalva obscures the anatomy in this area, especially when left anterior oblique views are taken. The right coronary artery, however, may be adequately visualized by aortography.[4]

Selective coronary arteriography in children including various techniques and approaches has been reported. In 1969, G. Formanek[5] presented five patients between the ages of 6 and 11 years who were studied by selective coronary arteriography. Between 1974 and 1979, 238 patients were studied by Parenzan[6] with the youngest patient being 5 months old. In 1980, Dabizzi[7] reported selective coronary arteriography in 119 patients from 5 months to 26 years in age with tetralogy of Fallot. A. Formanek's[3] series of 12 patients between 3 weeks to 16 years in age was published in 1980. Takahashi[4] described his technique of selective coronary arteriography in 1983. He reported on 34 cases in patients aged 7 months to 18 years. Reported series from France appeared in 1975 by Chaumont,[8] and in 1985 by A.M. Worms,[9] who reported selective coronary arteriography in 47 children performed between 1977 and 1983 with the age range of 1 to 13 years.

INDICATIONS FOR SELECTIVE CORONARY ARTERIOGRAPHY

Definition of the coronary artery anatomy in congenital heart disease may establish precise identification and diagnosis of specific conditions. Selective coronary arteriography helps in recognition of atrioventricular connections (concordance or discordance), as well as positions of cardiac chambers and interventricular septum.[1]

Diagnosis of congenital coronary artery anomalies and malformations depends on proper anatomic information obtained by selective coronary arteriography. These coronary artery anomalies

include anomalies of origin, course, or both.[1–7,9] These anomalies vary from major malformations with very significant clinical implications, including anomalous origin of the left coronary from the pulmonary artery,[10,11] to minor anomalies with little or no clinical importance.

Preoperative selective coronary arteriography serves as an important guide for the cardiac surgeon in the design and safety of a planned procedure. Preoperative assessment and knowledge of the coronary artery anatomy is particularly important when the goal is surgical repair and correction of specific conditions such as tetralogy of Fallot, double outlet right ventricle, and complete transposition of the great vessels.[1–7,9]

Various acquired diseases of the coronary arteries constitute another indication for the performance of selective coronary angiography.[9] These conditions include Kawasaki disease,[12] especially in view of its increased incidence; hypercholesterolemia of the familial homozygous type; various forms of inflammatory arteritis; and others.

Evaluation of myocardial ischemia[9] in the presence of chest pain or an abnormal exercise-test response will require selective coronary arteriography. This diagnostic tool may be part of a complete evaluation of dysrhythmias with significant clinical implications. Assessment of cardiac tumors[9] and cardiomyopathies includes selective coronary arteriography.

Postoperative selective coronary arteriography is indicated in many clinical situations,[9] for instance, following surgical treatment of anomalous origin of the left coronary artery from the pulmonary artery. Various techniques have been employed in treating this coronary anomaly in patients who have survived the early period of their life.[13,14] Patency and results of direct implantation of the left coronary on the aorta when feasible or saphenous vein bypass grafting of the left coronary artery with ligation of the proximal coronary artery should be assessed by selective coronary or graft injection. Selective coronary arteriography will show that the marked increase in size of the right coronary artery and the extensive collateralization from the right coronary artery to the left coronary artery will be reduced substantially following successful surgery.[13] Table 56–1 summarizes the indication for selective coronary arteriography in this age group.

TECHNIQUE OF SELECTIVE CORONARY ARTERIOGRAPHY

The technique of selective coronary arteriography varies according to the age of the patient. Although selective coronary arteriography has been performed in patients as young as 3 weeks, it is rarely performed in those under 1 or 2 years of age in whom aortic root injection is used. Different approaches[6] have been used, including femoral, axillary, humeral, and brachial, utilizing either percutaneous or cutdown techniques. For smaller children under age 5, size 4 or 5 French catheters with or without tapered tip are used. Catheter tips are usually formed just before the procedure.[3] The diameter of the terminal curve of the catheter should correspond to the width of the ascending aorta.[5] For the left coronary artery, an Amplatz-like catheter with a short tip (less than 5 mm) is appropriate.[4] The curvature of the catheter must approximate that of the aortic root. The short tapered tip is utilized to avoid wedging or subselective injection. For the right coronary artery, an "L" configuration is used.[4] The length of the ascending aorta and the diameter of the patient's aortic root are important factors in the selection of catheters.[4] These dimensions were found to be related to the height, body surface area, and age of the patients. In larger patients, Sones or Judkins catheters sizes 5 to 7 French with appropriate tip sizes can be used.[9]

Table 56–1. Indication for Selective Coronary Arteriography in Children and Adolescents

1. Precise definition of coronary artery anatomy for the diagnosis of congenital heart disease.
2. Precise diagnosis of congenital coronary artery anomalies and malformations.
3. Preoperative definition of the coronary artery anatomy, especially in specific conditions such as tetralogy of Fallot.
4. Acquired diseases of the coronary arteries.
5. Evaluation of myocardial ischemia.
6. Evaluation of cardiac tumors.
7. Evaluation of cardiomyopathies.
8. Evaluation of major ventricular dysrhythmias.
9. Postoperative evaluation of the coronary anatomy.

Safe performance of selective coronary arteriography in children requires adequate sedation. Various agents including promethazine (Phenergan), meperidine (Demerol), chlorpromazine (Thorazine), and fentanyl (Innovar) have been used in smaller children. In older patients, diazepam (Valium) or midazolam HCl (Versed) may be used.[4,9]

The use of anticoagulation in the form of heparin at a dose of 100 IU/kg is recommended.[9] Heparin can be administered either intra-arterially or intravenously. Following completion of the study, anticoagulation may be reversed by the use of protamine sulfate. Although atropine and lidocaine are not used routinely in adult selective coronary arteriography, their use in children undergoing this test is probably appropriate. Atropine is recommended at a dose of 0.01 mg/kg.[4]

If percutaneous technique is employed, arterial entry is made in the usual manner. The arterial needle must accommodate at least a 0.25-in. wire. A Teflon-coated "J" tipped wire is recommended. The wire must be flushed before and after each use to reduce potential clot formation. Once the wire has reached the abdominal aorta, appropriate size sheath and dilator are introduced into the artery. Heparin at the recommended dose is administered. The catheter is then introduced over the wire into the ascending aorta. The wire must not meet any resistance as it is traveling into the aorta. The operator should make every effort to minimize the time that a wire is in the arterial system. Following removal of the wire, blood is aspirated, and the catheter is connected to the manifold system. Arterial blood pressure is checked to confirm that the catheter tip is in the true lumen of the artery. A small test dose injection of the contrast material also will demonstrate that the catheter has not created a false channel. The closed manifold system is maintained at all times to obviate the need for removing the syringe and to decrease the inadvertent introduction of air emboli. The operator should not allow the catheter tip to engage into the aortic arch vessels as it is being advanced into the ascending aorta.

The catheter should be moved slowly and cautiously with constant monitoring of the blood pressure curve. For the left coronary artery cannulation, the LAO view provides easier recognition of the ostium of the coronary artery. The catheter is gently maneuvered into the left coronary sinus. The tip is guided upward toward

the left coronary ostium. Once the catheter is felt to be in the proper position, a very small test dose is given. This not only demonstrates proper catheter position, but also shows free flow and rapid clearance of the contrast material, proving that the catheter is not "wedged" and that injection can be made safely. The lumen of the catheter should be filled with contrast material at all times. Blood must not be allowed to back up into the catheter or the manifold. Once appropriate positioning of the catheter and free flow of the contrast material are ensured, injection is made, using adequate pressure to deliver the contrast material in a uniform fashion. Interrupted or weak injections are to be avoided. The duration and amount of injection depend on the size of the artery and the patient. An adequate injection spans three or four cardiac cycles. The right coronary artery is then approached, using a proper size catheter. The LAO view is a suitable view to start. If the catheter is moving freely, a gentle clockwise rotation will facilitate entry into the right coronary artery.

Careful monitoring of cardiac rhythm and hemodynamics is essential for the performance of safe selective coronary arteriography. Continuous pressure monitoring through the tip of the catheter except during injection of contrast material is mandatory. Such pressure monitoring will allow the operator to be aware of any "wedging" of the catheter into the coronary artery due to either mismatch of catheter size and coronary artery diameter or the presence of ostial narrowing. Frequently, subselective engagement of the catheter tip into a branch other than the main orifice of the coronary artery may be the cause of a pressure drop, as recorded by the catheter tip. This could prove to be a cause of potentially serious complications. The operator should ensure the presence of an air-free system, utilizing all precautions and proper procedure to avoid introduction of air emboli into the arterial system.

The dosage of contrast material injection and the number of injections[4] must be kept to a minimum without sacrificing the quality of the study. This goal can be achieved by the proper choice of angiographic views. Biplane coronary angiography utilizing appropriate angulations will limit the number of injections. Choice of a contrast agent depends on the operator's preference. Low osmolality ionic (ioxalate) or nonionic (iopamidol or iohexol) contrast media with adequate iodine concentration for better visualization is recommended.

In children, the number of angiographic positions and views used are fewer than in adults. Two LAO views (40 to 70°) of the left coronary artery, one of these in a cranial angulation, and a 30° RAO will be sufficient in most cases. The right coronary artery is imaged in LAO and RAO views.

PROBLEMS AND COMPLICATIONS

Difficulties and problems that may be encountered during the course of or following selective coronary arteriography are variable and secondary to a number of factors.[3–5,9] Arterial spasm, either in the brachial-axillary artery or the femoral artery, may lead to difficulty in manipulating the catheter and is uncomfortable for the patient. Once the catheter is in the ascending aorta, improper catheter size, configuration, or length of the catheter tip will impose difficulty in selectively engaging the coronary artery ostium. Caliber of the vessel in relation to the caliber of the catheter should be carefully noted. A catheter that is too large in diameter compared to the artery that is being cannulated will not only result in "wedging" of the catheter tip, but may prevent selective engagement altogether. A common pitfall that must be avoided while performing selective coronary arteriography is that of overlooking separate ostia. A conus branch occasionally has a separate ostium from that of the right coronary artery. In tetralogy of Fallot, the coronary ostia may not be where expected and are located in a more anterior-posterior position.

Complications associated with selective coronary arteriography in children and adolescents range from relatively minor to fatal.[3–5,9] The occurrence of a localized hematoma or bleeding is the same as with any arterial catheterization and should be minimized by using proper techniques. Arterial complications including occlusive thrombosis or dissection may require surgical intervention. Hypotension, which is usually transient, can be corrected with infusion of fluids, and will rarely require use of vasopressors. Arrhythmias including ventricular fibrillation or bradyarrhythmias may be noted, and appropriate forms of treatment must be readily available. A most serious complication is dissection or laceration of a coronary artery. This could happen as a result of inadvertent advancing of the catheter tip, resulting in injection of contrast material into the wall of the artery or one of the smaller branches. If a catheter has wedged into a branch and injection is made forcefully, dissection will easily develop. Abrupt movement by the patient is another factor that may lead to dissection. The operator must avoid excessive penetration of the catheter into the coronary arteries and should not allow the tip of the catheter to reach bifurcating or dividing positions. When retracting a catheter, especially if Amplatz-type curve is used, cautious practice requires this to be done under fluoroscopy, since the catheter tip tends to advance for a distance with the tip "scratching" the intima of the coronary artery as the catheter is being withdrawn. Death has been reported[3] due to a major coronary artery dissection.

CONGENITAL ANOMALIES OF THE CORONARY ARTERIES IN SPECIFIC CONDITIONS

Selective coronary arteriography is particularly indicated when surgical correction is planned. The results of surgery not only depend on the functional abnormalities involved, but also on the presence of certain unfavorable anatomic and coronary features. The course and distribution of the coronary arteries should be known prior to surgery to prevent division of an aberrant vessel. Since anomalous and aberrant coronary arteries are frequently undetectable during surgery, the inadvertent division of a large coronary branch during right ventriculotomy often results in major problems and even death. A vessel may be obscured by epicardial fat or by pericardial-epicardial adhesions from previous surgery, or by assuming an intramyocardial course. The possibility of serious complications is reduced when the preoperative coronary anatomy is known. Even with such information, the surgical approach cannot always be free of hazards. The distribution of the coronary arteries over the anterior surface of the right ventricle is of particular importance when surgery is anticipated.

Selective Coronary Arteriography in Patients with Tetralogy of Fallot and Double Outlet Right Ventricle

The true incidence of coronary anomalies in tetralogy of Fallot is not firmly established. Reported frequency of coronary anomalies varies according to the method of study. Four different meth-

ods have been used to assess the incidence of coronary anomalies in tetralogy of Fallot: 1) intraoperative inspection,[15] 2) necropsy examination,[16,17] 3) aortography or ventriculography,[18] and 4) selective coronary angiography.[7]

Various series[15,19–22] including a large series of 1,400 cases[15] are reported from 1959 to 1975. The incidence of a coronary anomaly detected at the time of surgery varied between 2 and 19%. When the anterior descending coronary artery originated from the right coronary artery, a 30% mortality due to myocardial infarction was reported in the series by Berry.[15] His series showed a 2% incidence of coronary anomaly detected intraoperatively.

Incidence of coronary artery anomaly at necropsy was found to be between 4 and 9%.[16,17]

A 6 to 12% incidence of coronary anomalies has been found when angiographic data have been utilized.[7,18]

In 1980, Dabizzi[7] reported on 119 patients with tetralogy of Fallot. All patients had selective coronary arteriography. A 9% incidence of major anomalies and a 19.3% incidence of a large conus branch were found. McManus et al.[23] looked at the combination of all methods and found a 3% overall incidence of anomalous coronary arteries.

The most important coronary artery anomalies in tetralogy of Fallot, as determined by various methods of detection,[15,23] are listed in Table 56–2.

In double outlet right ventricle, the origin of the anterior descending coronary artery may be from the right coronary artery.[24]

Complete Transposition of the Great Arteries

Anomalies of the coronary arteries in complete transposition have been described by several authors.[25,26] Coronary artery anatomy in complete transposition has multiple patterns.[27] The most common variations are

1. Origin of the left coronary artery from the left sinus and the right coronary artery from the posterior sinus.
2. Origin of the right coronary artery and the left circumflex from the posterior sinus and the anterior descending from the left sinus.
3. Single coronary artery from the posterior or left sinus.

In congenitally "corrected" transposition, the coronary arteries are inverted compared to normal. Accurate knowledge of the coronary arterial tree is important when a Mustard, Rastelli, or any other procedure is planned. Various surgical injuries to a major coronary artery branch have been described.[28] The presence of pericardial fibrosis from previous surgery may further obscure the anatomy, especially if an incision has to be made in the anterior surface of the right ventricle. Inadvertent ligation, occlusion or division of a major coronary artery can happen during a Rastelli procedure. Lesions of the sinus node artery in complete transposition undergoing Mustard procedure have been noted, resulting in sinus node dysfunction. Preoperative selective coronary arteriography is recommended to decrease the incidence of surgical trauma to a major coronary artery branch.

Table 56–2. Coronary Artery Anomalies in Tetralogy of Fallot

1. The anterior descending artery originating from the right coronary artery or the right sinus of Valsalva.
2. Single coronary ostium, either single left coronary or single right coronary.
3. The left circumflex origin from the right coronary artery.
4. The presence of a large conus branch, which should be differentiated from the anterior descending artery. This is a frequent finding in tetralogy of Fallot, probably as a response to right ventricular hypertrophy.
5. Fistulas between the coronary arteries and the pulmonary artery or the right atrium.
6. Connections between coronary and bronchial arteries.
7. Right coronary artery from the pulmonary trunk.
8. Hypoplastic coronary arteries.
9. Separate origin of the conus artery from the aorta.
10. Complete intramyocardial course of the anterior descending artery (7% of all cases).

Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery

The anomalous origin of the left coronary artery from the pulmonary artery was first described in 1908.[29] The clinical course of this anomaly depends on the presence and development of collateral circulation. In the majority of patients, symptoms appear in the first few months of infancy and result in myocardial infarction, congestive heart failure, or death.[13] However, patients with extensive collateral circulation will reach adulthood and may even lead an asymptomatic, normal life. Selective coronary arteriography reveals the presence of a large right coronary artery, which supplies extensive collateral circulation to the left coronary artery (Figs. 56–1 and 56–2).

The left coronary artery, which drains into the pulmonary artery, is visualized with the injection of contrast material into the right coronary artery. Corrective surgery, whether direct implantation

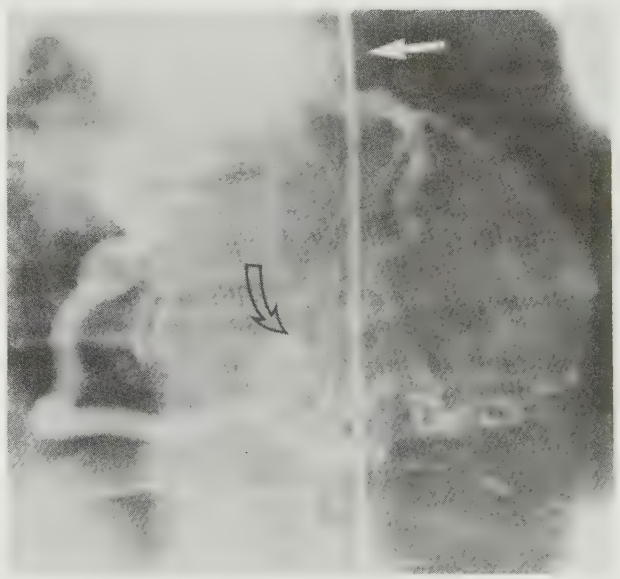

Fig. 56–1. Selective injection of contrast material into the right coronary artery showing a very large and redundant vessel opacifying the left coronary artery through collaterals (black arrow). White arrow visualizes the attachment of the left coronary artery to the pulmonary artery.

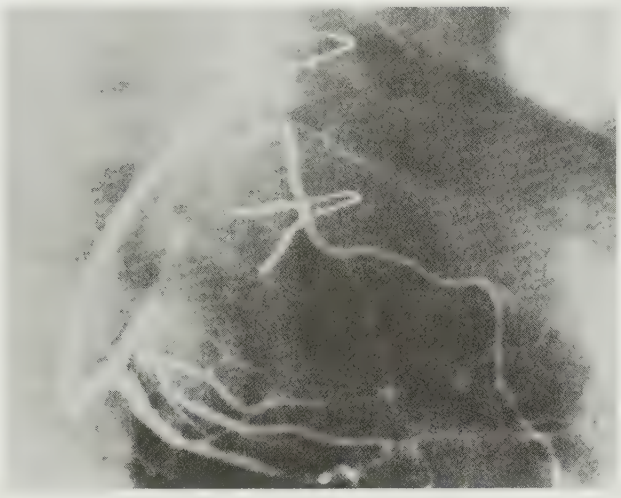

Fig. 56–2. Selective right coronary arteriography reveals marked decrease in size and redundancy of this vessel. No collaterals to the left coronary artery are visualized.

of the left coronary artery on the aorta or bypass grafting, will result in gradual normalization of the right coronary artery size and angiographic disappearance of the collateral vessels (Fig. 56–3).

ACKNOWLEDGMENT

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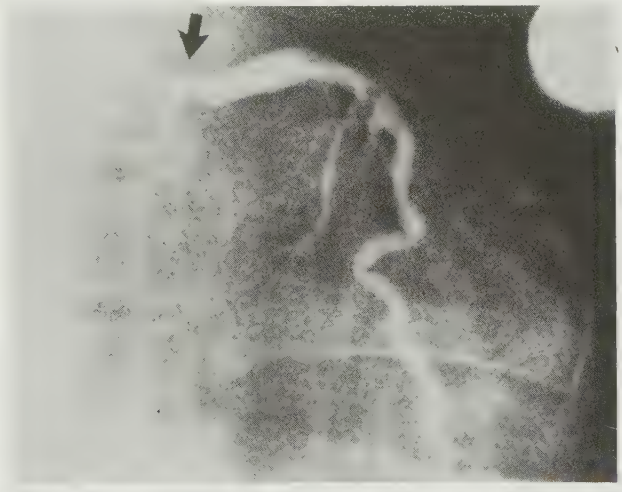

Fig. 56–3. Selective coronary arteriography shows patent and smooth implantation site (arrow) with normal left anterior descending and circumflex arteries.

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CHAPTER 57

Peripheral Vascular Angiography

Mark D Skolkin

The first radiographic demonstration of a human blood vessel was obtained in 1896, only months after the discovery of x-ray energy by Wilhelm Conrad Roentgen.[1,2] Since that time, countless evolutionary steps have resulted in the highly sophisticated field of peripheral vascular angiography as we know it today. Perhaps the most significant contribution was the introduction of percutaneous transfemoral catheterization by Seldinger in 1953.[3]

Image-intensified fluoroscopy, mechanical contrast injectors, and high-speed film-screen combinations that allow the acquisition of at least three films per second are basic requirements of the imaging suite. Small-focal-spot x-ray tubes (0.1 to 0.3 mm in diameter) are essential for the performance of high-quality magnification radiography and for imaging small vessels in sharp detail.

Digital subtraction angiography (DSA) is a technique by which images taken prior to contrast injection are electronically subtracted from those acquired after administration of a contrast bolus so that only vascular structures are displayed. The major advantage of DSA in comparison with conventional film angiography is its increased contrast sensitivity. Conventional angiography requires a contrast concentration of approximately 40 to 50% within a blood vessel to obtain a satisfactory image, while DSA requires only 2 to 3%.[4] Major drawbacks to the technique are decreased spatial resolution with resultant loss of image detail and degradation of the image by respiratory, peristaltic, cardiovascular, or voluntary motion.

Intra-arterial DSA is performed in the same manner as conventional film angiography. However, only one-fifth to one-third the amount of contrast material is necessary. Intravenous DSA usually requires the placement of a central venous catheter and injection of approximately 1 mL/kg of body weight of contrast material for each run—a considerable increase over conventional intra-arterial angiography for most studies. Therefore my colleagues and I rarely use intravenous DSA, with notable exceptions being the study of central veins and use in patients in whom arterial access cannot be obtained.

State-of-the-art radiographic equipment can produce excellent images only in relatively motionless subjects. For this reason, we prefer to use general anesthesia in all children less than 10 years of age; older children are evaluated for use of local versus general anesthesia on an individual basis.

In the first 2 weeks of life, the umbilical artery may be recanalized for the performance of peripheral vascular studies, particularly in the investigation of congestive heart failure related to neonatal hepatic masses. Injection of contrast through umbilical artery catheters, which are used to monitor critically ill neonates, is helpful in detecting complications related to their placement, including thrombosis, embolism, or aneurysm formation. Needles and basic guidewires used in femoral artery catheterization are shown in Figures 57–1 and 57–2. My colleagues and I perform the puncture with a 21-gauge Argon needle (Argon Medical Corp., Athens, TX) in children under 4 to 5 years old. This needle will allow introduction of a 0.021-in. Teflon-coated guidewire into the femoral artery, over which graduated dilation of the puncture site with 20- and 18-gauge intravenous cannulae (Argyle Medicutt, Tullamore, Ireland) is performed. In older children, an 18-gauge thin-walled needle (Cook Company, Bloomington, IN) is used, through which a 0.035-in. guidewire is threaded.

Catheter shapes routinely employed in our department are shown

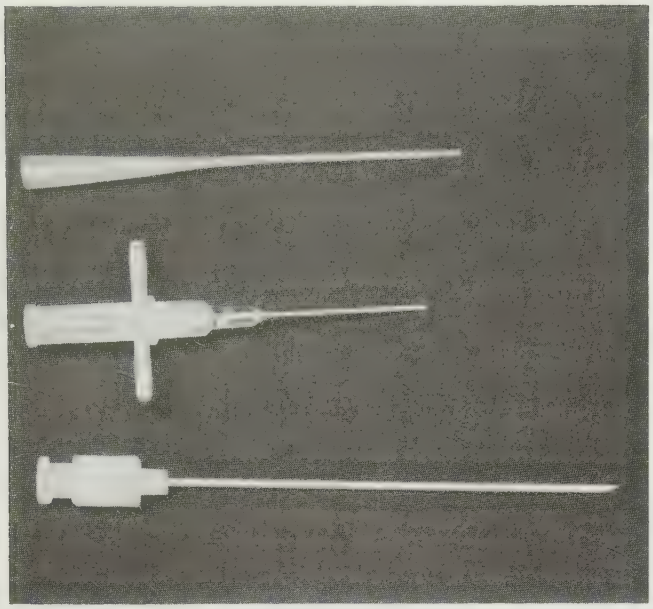

Fig. 57–1. Needles and cannulae used in femoral puncture. Top to bottom: intravenous cannula (18- and/or 20-gauge), 21-gauge Argon needle, 18-gauge thin-walled needle.

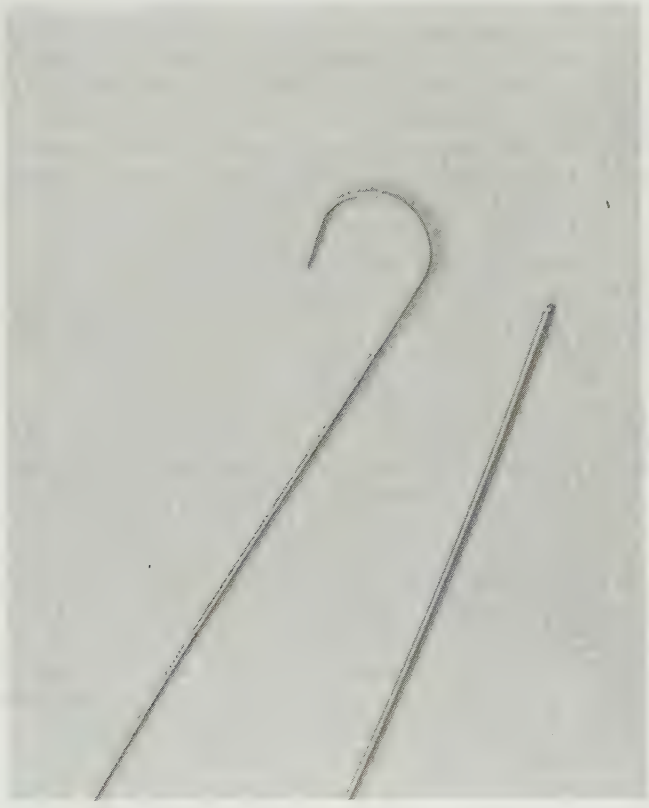

Fig. 57–2. Basic guidewires. Left: J-shaped guide; the radius of curvature is commonly 1.5, 3.0, or 15.0 mm. Right: straight guide.

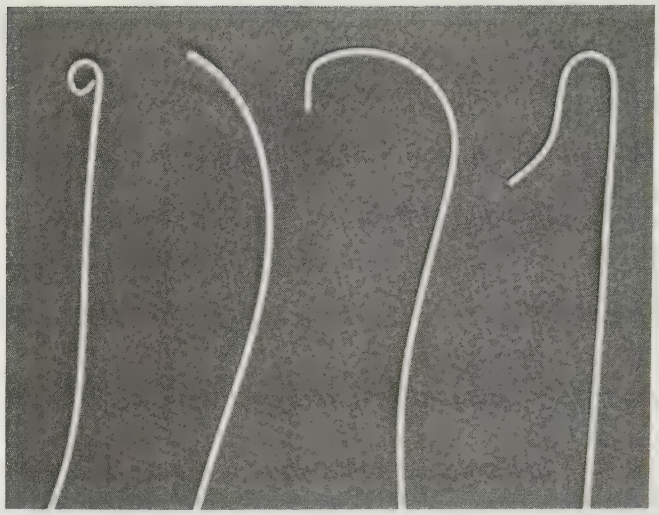

Fig. 57–3. Basic catheter shapes. From left to right: pigtail, simple curve, cobra, reverse curve (shepherd's crook).

in Figure 57–3. The smallest catheter that can accomplish the objectives of the study is chosen. For aortography 4 or 5 French pigtail catheters are appropriate; simple curve, cobra curve, or reverse-curve shapes are suitable for selective catheterization. Approximate contrast injection and filming rates are listed in Table 57–1.[5,6]

Radiographic contrast agents are water-soluble triiodinated benzoic acid derivatives. The recently introduced low-osmolality agents exist in both ionic and nonionic forms; osmolality is approximately one-half that of conventional compounds at the same iodine content (Table 57–2).[7] Theoretically, lower osmolality should decrease fluid shifts and other cardiovascular side effects. However, existing clinical data are unclear on this point as well as on the relative incidence of allergic-type reactions and nephrotoxicity.[8–10] A reported disadvantage of these newer compounds is their poor anticoagulant action, which necessitates frequent flushing of the catheter to prevent the formation of small thrombi.[11,12]

Embolic agents most frequently used in our department are gelfoam, polyvinyl alcohol foam (Ivalon), and stainless steel coils. Gelfoam is supplied in a sheet-like sponge, which may be cut into pledgets approximately the size of the vessel. Occlusion is usually temporary. Permanent occlusion may be achieved with Ivalon (particles and pledgets) or coils. A further discussion on occlusive materials and techniques may be found in Chapter 85.

Angiography is contraindicated in children in whom diagnosis and therapy can be based on information obtained noninvasively. It should be avoided in the ecchymotic subgroup of Ehlers–Danlos syndrome, as arterial rupture may occur from seemingly minor catheter or guidewire trauma.[13,14] Patients in the other four subgroups of this disorder may be approached carefully; up to four arteriographic studies have been reported in a patient with the mild variety without sequelae.[15] Studies in individuals with homocystinuria are relatively contraindicated because of the possibility of arterial thrombosis.[16,17]

The risks of catheterization for the purpose of peripheral vascular studies are small, particularly when performed by an experienced pediatric angiographer. The most common untoward effect is transient spasm at the femoral puncture site, with devel-

Table 57–1. Approximate Contrast Dosages and Filming Rates

	Contrast Dose in ml					
	10 kg	*10 to 20 kg*	*20 to 40 kg*	*40 kg (in ml/kg)*	*Injection Duration (sec)*	*Filming Rates (Films per sec/ no. of sec)*
Aorta, arch	8–15	15–30	25–50	0.8–0.9	2.0	3/2:1/4
Aorta, abdominal	8–15	15–30	25–50	0.8–0.9	1.5–2.0	3/2:1/4
Celiac axis	5–10	10–20	20–40	0.8	5.0–6.0	2/5:1/5:0.5/10*
Hepatic or splenic	4–8	8–15	15–25	0.5	5.0–6.0	2/5:1/5:0.5/10
Renal	1–2	3–5	5–7	7–9	1.2–1.5	3/2:1/4:0.5/10
Superior mesenteric	5–10	10–18	18–32	0.7	5.0–6.0	2/5:1/5:0.5/10
Inferior mesenteric	3–7	5–10	10–20	0.4	5.0–6.0	2/5:1/5:0.5/10

*0.5/10 represents one film obtained every other second over a 10-sec period. Adapted from Kirks et al.[5] and Stanley and Miller.[6]

opment of a pale, cool lower extremity; peripheral pulses are usually not palpable. At our institution, children who develop this side effect are approached conservatively. The involved extremity is kept warm, and systemic heparinization is initiated at a dose of 75 to 100 units/kg, which is given as an intravenous (IV) bolus. The partial thromboplastin time is maintained at approximately two times normal, with IV heparin given every 4 to 6 hours, and peripheral circulatory status is monitored with Doppler ultrasound. Surgical exploration of the femoral artery is rarely necessary, as most pulses return to normal within 24 hours.

Thrombosis at the arterial puncture site is less commonly observed since the advent of smaller catheters and refinement of percutaneous catheterization techniques. There may be an association between thrombosis and subsequent growth retardation of the lower extremity, particularly when it occurs at an early age.[18,20]

Children with coagulopathies or severe hypertension are at risk for bleeding from the puncture site. Clotting disorders should be corrected before arteriography is performed. Pharmacologic control of blood pressure is important in hypertensive children, particularly when large catheters are used to perform renal angioplasty.

Adverse effects of contrast injection include renal insufficiency, congestive heart failure, and allergic-type reactions. Contrast-induced renal dysfunction is most likely to occur in the setting of preexisting renal disease or concomitant administration of a nephrotoxic drug. Contrast toxicity can generally be avoided by limiting the volume to a maximum of 4 mL/kg of body weight and ensuring good hydration. Allergic reactions range from mild urticaria to life-threatening cardiovascular collapse and are more common in children with a history of asthma. Individuals with a documented mild reaction to contrast media may be premedicated with diphenhydramine (Benadryl) in a dosage of 5 mg/kg intramuscularly 30 min before the study.[21] If the reaction is severe, every attempt should be made to obtain the desired information noninvasively, using computed tomography, ultrasound, and/or magnetic resonance imaging. As a last resort, angiography with one of the newer low-osmolarity contrast agents and following pretreatment with prednisone (2 mg/kg daily for 3 days) may be performed.

Risks of transcatheter embolization, vasopressin infusion, and balloon dilatation are discussed later in the chapter.

Table 57–2.

Contrast Agent	*Iodine Content (mg/mL)*	*Osmolality (mOsm/kg H_2O)*
Diatrizoate (Renografin 60)	282	1511
Diatrizoate (Renografin 76)	370	1689
Iothalamate (Conray)	282	1217
Ioxaglate (Hexabrix)	320	580
Iohexol	280	620
Iohexol	370	980
Iopamidol	280	570
Iopamidol	370	796

Adapted from Bettmann.[7]

THORACIC AORTA—GENERAL CONSIDERATIONS

The thoracic aorta and great vessels are the product of fusions and regressions of the paired dorsal aortae and aortic arches. A detailed embryologic discussion of this process can be found elsewhere.[22] The "normal" aortic arch courses posteriorly and to the left at the level of the fourth thoracic vertebral body, giving rise to the brachiocephalic, left common carotid, and left subclavian arteries. The most prevalent variation is a common origin of the brachiocephalic and left common carotid vessels, which occurs in nearly one of four individuals. Direct origin of the left vertebral artery from the aortic arch rather than from the subclavian artery occurs in up to 6% of the general population.[23] Discussion here of abnormalities of the thoracic vasculature will be limited to Takayasu's arteritis, systemic arteries to the lung (bronchopulmonary sequestration and bronchial arteriography), aortic trauma, and structural diseases that result in aortic aneurysm; thoracic aortic coarctation and complex cardiovascular disorders that involve the aorta are covered in other chapters.

Takayasu's Arteritis

Takayasu's arteritis is a granulomatous giant-cell arteritis of the aorta and its large branches, which contain abundant mural elastic fibers. Pulmonary arterial involvement has been reported in 50 to 80% of cases.[24] Pathologically, there are transmural inflammatory alterations that are most pronounced in the intima, where marked thickening and fibrosis is found.

Takayasu's disease is found worldwide, although it is more prevalent in Southwest Asia, Japan, and Africa. It occurs most frequently in women (80 to 90% of the reported cases) in the second and third decades of life.[25,26] Two clinical phases are recognized. In the acute phase, patients often complain of constitu-

tional symptoms (fever, fatigue, malaise, anorexia) and migratory large-joint arthritis. These symptoms typically diminish over several weeks. The chronic phase is manifest months to years later, with cardiovascular and neurologic symptomatology. Hypertension and decreased carotid and upper extremity pulses and bruits in the neck and abdomen are commonly found on physical examination. Both right- and left-sided heart failure may occur and are related to pulmonary arterial or systemic hypertension, aortic insufficiency, and/or myocarditis.

Cardiomegaly and contour irregularity of the aortic arch and descending thoracic aorta with areas of dilatation or frank aneurysm formation may be found on chest roentgenography.[27] Angiography remains pivotal in establishing the diagnosis of Takayasu's disease. In most individuals, arterial DSA of the aortic arch in the right posterior oblique projection and abdominal aorta in the anteroposterior and lateral projections is performed. Evaluation of the pulmonary circulation should also be performed. In individuals unable to cooperate fully or with large amounts of bowel gas, biplane conventional angiography of the thoracic and abdominal aortae is appropriate.

Stenoses are the most common angiographic feature and vary from smooth, concentric to irregular, eccentric lesions.[28] Prestenotic and poststenotic aneurysms, luminal contour irregularity, and branch artery occlusions are commonly observed (Fig. 57–4). Well-recognized collateral pathways circumvent foci of narrowing or occlusion. The arteries most frequently affected are the left subclavian (in 85 to 95% of cases), renal (75%), abdominal aorta (greater than 50%), pulmonary (greater than 50%), superior mesenteric, thoracic aorta, brachiocephalic, left carotid, and celiac.[26,28] Stenoses of the great vessels and visceral arteries usually occur at or just distal to their origins. Long-segment fusiform stenosis of the descending thoracic and midabdominal aortae rarely progress to total occlusion; the inferior mesenteric artery may become markedly enlarged in the latter instance (see Fig. 57–9).

A firm diagnosis of Takayasu's arteritis can be established in the great majority of cases by integration of the angiographic and clinical pictures. Isolated renal arterial stenoses, however, are difficult to differentiate from those related to neurofibromatosis, fibromuscular dysplasia, and other vasculitides.[27]

Prognosis in this disease is guarded, with a tendency toward chronicity and gradual deterioration.[29] Death is most frequently attributable to heart failure or cerebral complications. The current mainstay of therapy is oral prednisone; intravenous cyclophosphamide has proven beneficial in some cases.[26,30]

Surgical bypass may be performed in individuals in whom severe steno-occlusive lesions result in unacceptable limitation of function or are life threatening. Failure of this procedure may ensue, however, when progressive arteritis produces stenosis at or adjacent to the proximal or distal anastomoses. Recently, percutaneous transluminal dilatation of stenoses has been performed with encouraging results. Renal angioplasty in this disease will be discussed later in this chapter. Carotid, mesenteric, and subclavian lesions have also been successfully dilated.[31] Transluminal dilatation, even if unsuccessful, rarely precludes subsequent operative intervention.

Bronchopulmonary Sequestration

Bronchopulmonary sequestration is a relatively rare developmental abnormality that results in a cystic mass of nonfunctioning lung tissue that lacks normal communication with the tracheo-

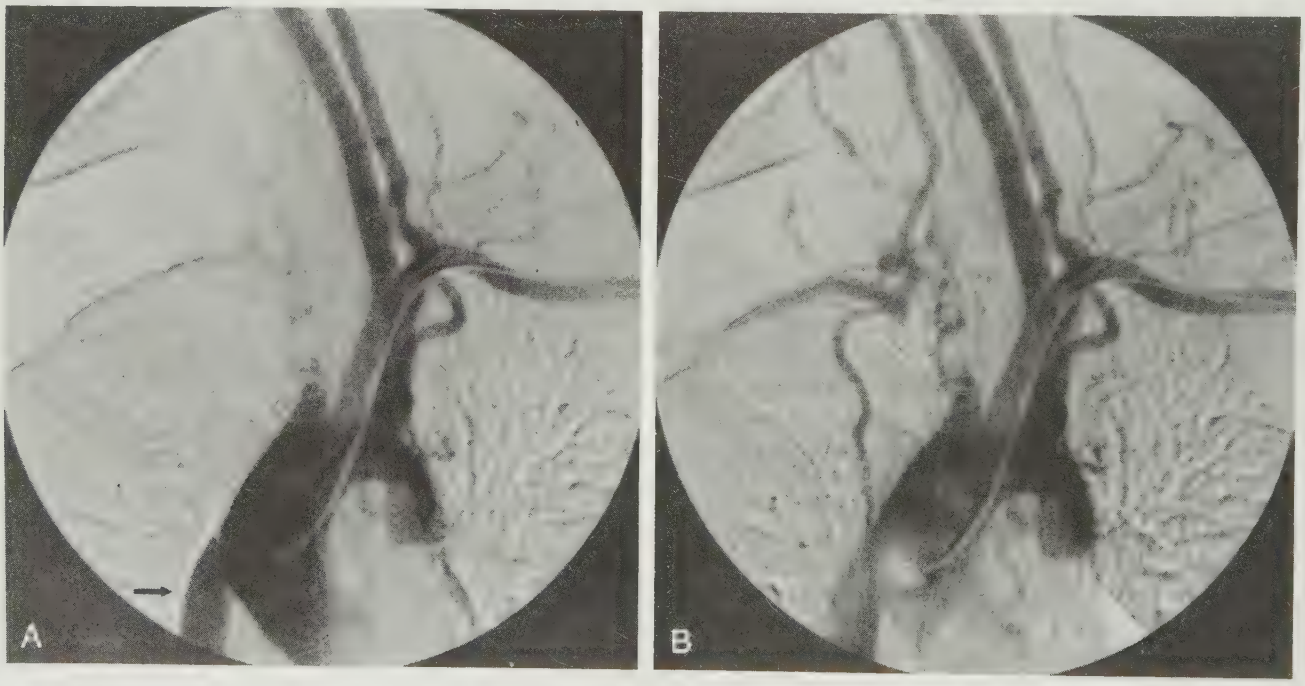

Fig. 57–4. DSA of 16-year-old with Takayasu's disease. (A) Early arterial phase with occlusion of the brachiocephalic artery just distal to its origin and the proximal descending thoracic aorta and marked enlargement of the left vertebral artery. Note graft projected to the right of the ascending aorta (arrow), which is anastomosed distally to the abdominal aorta. (B) Late arterial phase. Retrograde flow down the right vertebral artery has resulted in a "subclavian steal" phenomenon. Enlargement of the internal mammary arteries to supply collateral flow to the lower extremities is also seen.

bronchial tree and receives all or most of its blood supply from anomalous systemic arteries. The more common form of this entity is the intralobar variety, in which the sequestered lung is invested within the visceral pleural lining of the normal adjacent lung. There is a predilection for the lower lobes, although the lesion may be found in the upper lobes[32] or, rarely, bilaterally.[33] It is frequently discovered during the investigation of recurrent pneumonia. In a review of nearly 400 cases, aberrant arteries from the thoracic and abdominal aortae were observed in 74% and 19% of cases, respectively.[34] Pulmonary venous drainage has been reported in more than 95% of cases.[35]

In the extralobar form, the sequestration is contained in a separate pleural envelope, which isolates it from the adjacent lung. Associated complex congenital anomalies are present in up to 50% of cases.[34,35] Descending thoracic (46%) and abdominal (32%) aortic, as well as pulmonary (5%) and intercostal (4%) arterial blood supply was noted in the series of Savic et al.[34] Venous return is usually via systemic veins (particularly, the azygous and hemiazygous systems), although pulmonary or dual pulmonary and systemic venous drainage may be observed infrequently.

Chest roentgenography reveals a solid or cystic-appearing soft-tissue mass. Computed tomographic examination will better define its relation to the mediastinum and surrounding lung; visualization of the anomalous artery on contrast-enhanced studies has been reported.[36,37] Thoracic aortography with subsequent selective injection of the feeding vessel remains the procedure of choice in the presurgical evaluation of these children (Fig. 57–5). Filming is always carried out to the venous phase, which generally occurs quite rapidly, with frank arteriovenous shunting in some cases. The feeding artery averages 6 to 7 mm in diameter; multiple vessels are present in at least 15% of cases.[34] Definitive angiographic distinction between intralobar and extralobar varieties is not possible in some individuals because of the overlap in venous drainage patterns. We do not routinely perform pulmonary arteriography;

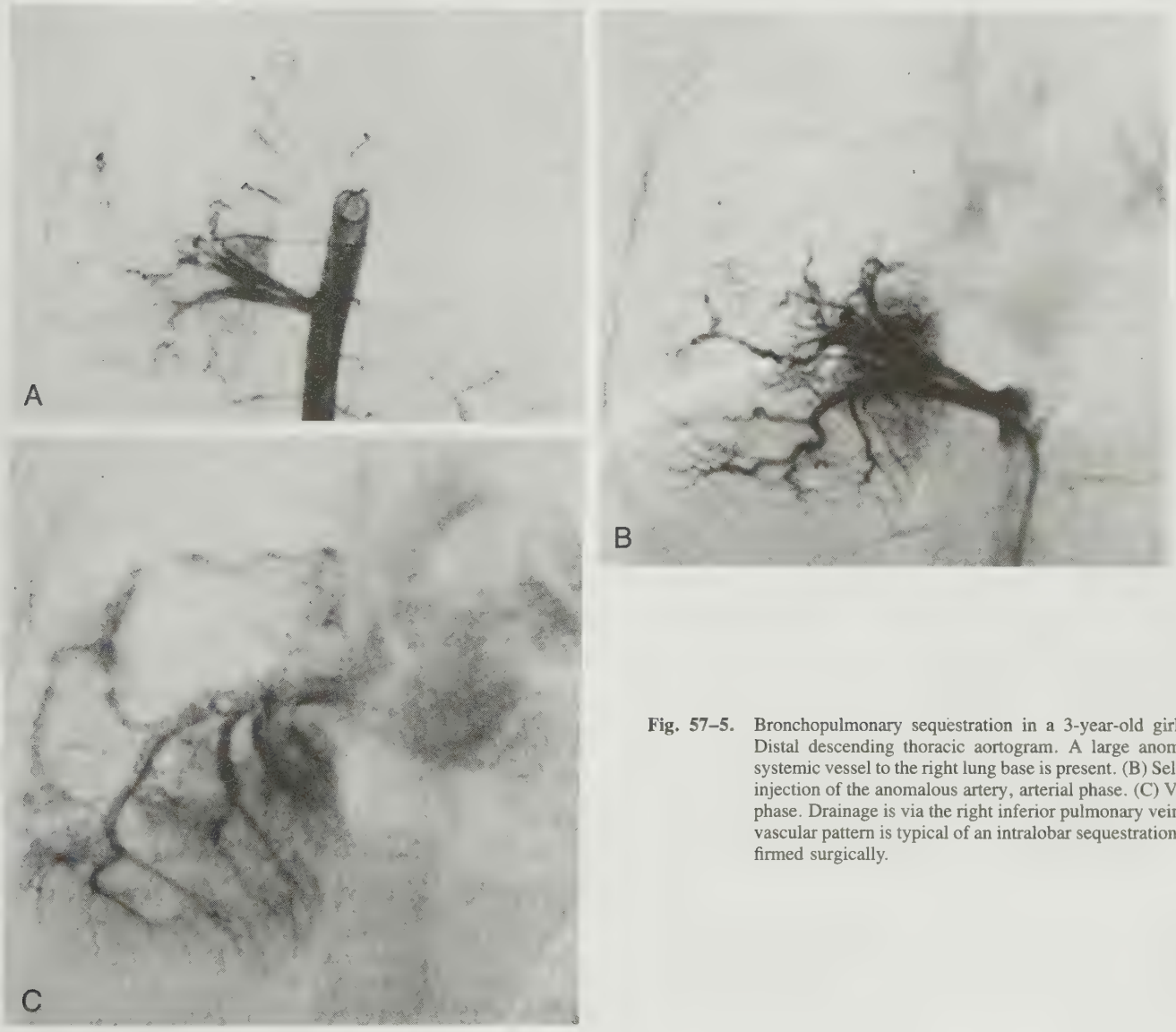

Fig. 57–5. Bronchopulmonary sequestration in a 3-year-old girl. (A) Distal descending thoracic aortogram. A large anomalous systemic vessel to the right lung base is present. (B) Selective injection of the anomalous artery, arterial phase. (C) Venous phase. Drainage is via the right inferior pulmonary vein. The vascular pattern is typical of an intralobar sequestration, confirmed surgically.

however, it is of potential benefit in the few cases in which the systemic vasculature does not appear to supply the entire soft-tissue or cystic mass.

Treatment of this entity is segmental or lobar resection, and prognosis is excellent. Untreated cases run the risk of recurrent pneumonias, hemorrhage, or, rarely, congestive heart failure secondary to arteriovenous shunting.

Bronchial Arteriography and Embolization

Massive hemoptysis (more than 300 mL of blood in a 24-hr period) in patients with advanced pulmonary disease of cystic fibrosis results from erosion of enlarged bronchial arteries found in areas of bronchiectasis and is potentially a life-threatening problem.[38] Resection of the bleeding segment is not optimal in these patients with limited pulmonary reserve, neither is it always possible to localize the bleeding site preoperatively by bronchoscopy or radionuclide studies.[39] Transcatheter embolization offers the advantages of prompt cessation of bleeding and commencement of vigorous pulmonary physical therapy within 24 to 48 hr.[40]

Bronchial arteries are quite variable in number and position but usually arise from the anterior or anterolateral aspects of the descending thoracic aorta just distal to the origin of the left subclavian artery. The most constant vessel is the intercostobronchial trunk to the right upper lobe. Care must be taken in occluding this vessel as it is known occasionally to supply radicles to the anterior spinal artery.[41]

Arterial DSA of the descending thoracic aorta is first performed to localize the enlarged bronchial arteries, which are subsequently selectively catheterized. Use of low-osmolarity contrast agents decreases the urge to cough due to bronchial irritation and limits potential neurotoxicity if arteries to the spinal cord are present.

The most commonly observed angiographic feature is the presence of bronchial-to-pulmonary-artery shunting (Fig. 57–6); it is quite unusual to demonstrate active extravasation.[40] We occlude all enlarged bronchial arteries in which a catheter can be well seated; a reverse-curve shape has been the most effective for this purpose. Injection of small particles of gelatin (e.g., gelfoam) pledgets is terminated when stagnant flow in the vessel is achieved. Ethanol should not be used, as it causes intense pain and carries the risk of bronchial necrosis and injury to the spinal cord.[42] The postembolization syndrome consists of temperature to 101°F for 24 to 72 hr and chest-wall pain, which is probably related to occlusion of small mediastinal and intercostal arteries.[40] Massive hemorrhage is arrested quickly in the vast majority of children. However, the incidence of rebleeding is high, and approaches 50% at our institution within the first year. Repeat embolizations are performed as deemed clinically appropriate; we have followed patients for up to 8 yr with this approach. The nonbronchial systemic arteries of the lung become increasingly important with each procedure, particularly branches of the subclavian, axillary, intercostal, and phrenic arteries.[43,44] Care must be taken to ensure that, if the posterior intercostal arteries and thyrocervical trunk are to be sacrificed, they do not supply the spinal cord.

Aortic Trauma

Survival after blunt trauma to the thoracic aorta and great vessels hinges on an aggressive approach to the diagnosis and treatment of these injuries. Emergent thoracic aortography should be performed on patients who have evidence of a mediastinal hematoma on chest roentgenography after a deceleration injury, severe fall, or crushing blow to the chest.[45]

The examination is performed from a femoral artery approach, with a J-shaped guidewire placed into the ascending aorta, over which a pigtail catheter is threaded. Adverse effects of traversing an aortic injury from below are rare as long as the wire is redirected if it appears to get caught on an intimal flap and if power injection of contrast is never performed at the site of suspected transection.[46] Two views of the aorta, preferably the right posterior oblique and anteroposterior or left posterior oblique projections, are obtained. The pigtail catheter is always straightened with a wire before being retracted through an aortic laceration. High-quality intra-arterial DSA is adequate to rule out an aortic injury[47]; conventional angiography should be performed in patients who are unable to cooperate fully or in clarifying any possible abnormality found on DSA.

Classically, transection occurs at the aortic isthmus, which is located just distal to the left subclavian artery. Injuries of the ascending and descending thoracic aorta and origins of the great vessels are observed infrequently.[45,48] Arteriographically, transection usually manifests as a false aneurysm or intimal flap at the aortic isthmus (Fig. 57–7). Rarely, extravasation is observed. Care must be taken not to confuse a ductus diverticulum with an acute injury; the former is recognized by a smooth transition with the adjacent aorta and no evidence of intimal disruption.

Children with penetrating injuries to the thoracic aorta and brachiocephalic arteries typically are taken directly to surgery, without angiographic evaluation. In the largest series in the literature, only 1% of patients had angiography before surgical exploration.[49]

Aortic Aneurysms

Aortic aneurysms are most frequently related to structural weakness of the aortic wall as in the Marfan or Ehlers–Danlos syndromes, or are inflammatory (mycotic) in origin. Marfan syndrome is inherited as an autosomal dominant trait or occurs as a spontaneous mutation. The predominant clinical features are arachnodactyly, lens dislocations, and cardiovascular abnormalities. The primary defect is abnormal collagen synthesis with resultant cystic medial necrosis of the ascending aorta and aneurysm formation, dilatation of the sinuses of Valsalva, and/or aortic regurgitation. The central pulmonary arteries may enlarge diffusely and myxomatous degeneration of the mitral valve results in the "floppy"-valve syndrome.[50]

Ehlers–Danlos syndrome is another manifestation of defective collagen synthesis, of which there are five identifiable clinical subtypes. Laxity of the skin, bruising, and hyperextensibility of the joints are integral features of the syndrome. Virtually every artery in the body, including the aorta, may undergo aneurysmal dilatation and progress to rupture.[13,15] The ecchymotic subtype is particularly prone to developing complications from angiography and should be approached carefully in this regard.

Mycotic aneurysms are often heralded by the sudden appearance and rapid enlargement of a mediastinal or abdominal mass. The most commonly isolated organisms are streptococcus, staphylococcus, pneumococcus, and salmonella.[51] The focus of infection is usually set up at points of turbulence or intimal injury rather than being related to invasion of the aortic wall from a contiguous focus. The most common site of involvement is the descending thoracic aorta, often distal to aortic coarctation or adjacent to the

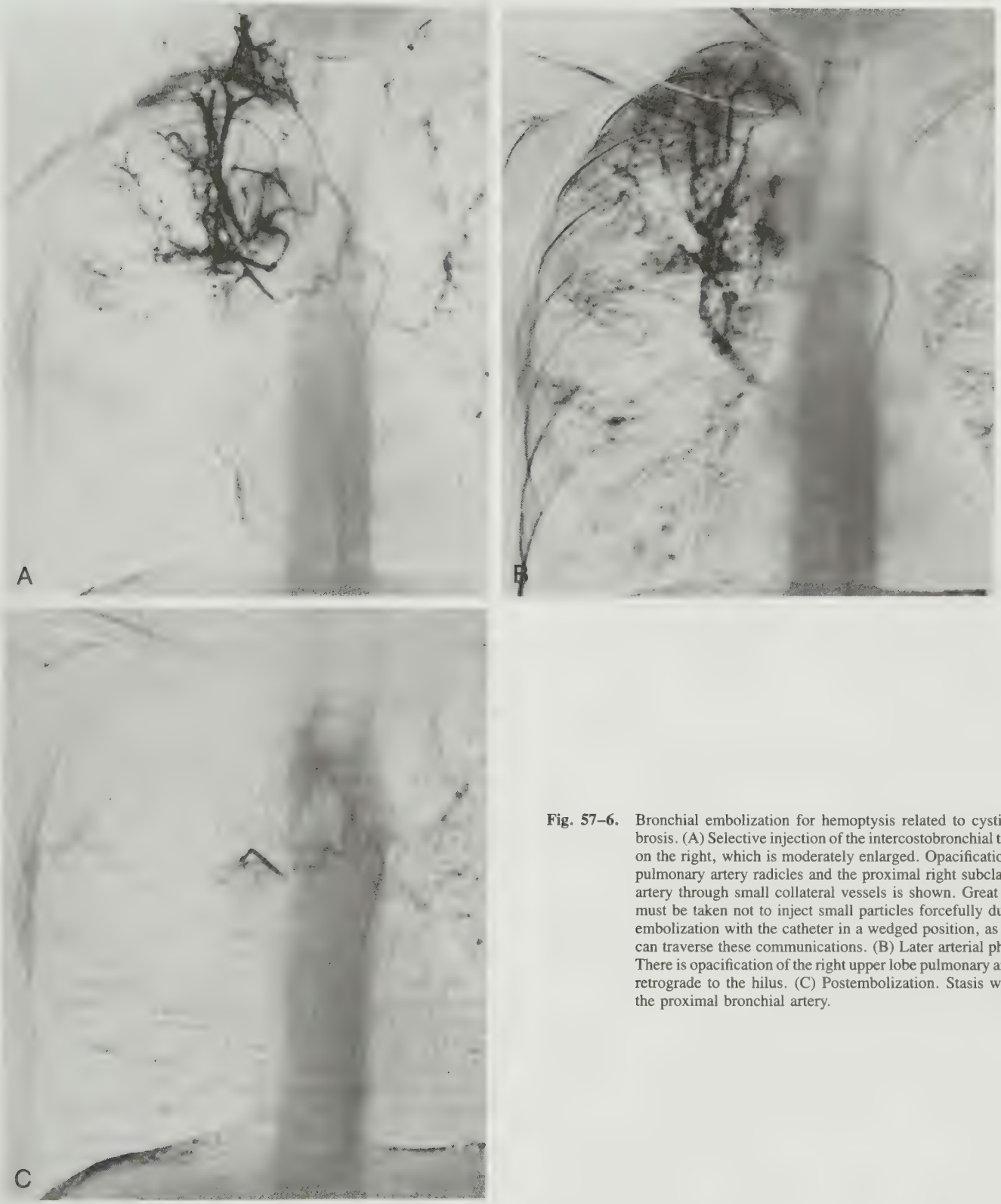

Fig. 57–6. Bronchial embolization for hemoptysis related to cystic fibrosis. (A) Selective injection of the intercostobronchial trunk on the right, which is moderately enlarged. Opacification of pulmonary artery radicles and the proximal right subclavian artery through small collateral vessels is shown. Great care must be taken not to inject small particles forcefully during embolization with the catheter in a wedged position, as they can traverse these communications. (B) Later arterial phase. There is opacification of the right upper lobe pulmonary artery retrograde to the hilus. (C) Postembolization. Stasis within the proximal bronchial artery.

Fig. 57–7. DSA of the aortic arch in the right posterior oblique projection, showing a typical traumatic false aneurysm arising from the aortic isthmus. A common origin of the brachiocephalic and left common carotid arteries is present, a normal variant.

tip of an umbilical arterial catheter (Fig. 57–8).[51–53] It is preferable to avoid direct injection of contrast into the aneurysm as a shower of peripheral septic emboli may result.

Other causes of aortic aneurysms include syphilis, prestenotic and poststenotic dilatation associated with coarctation, and trauma.

ABDOMINAL AORTOGRAPHY

The abdominal aorta is the direct continuation of the thoracic aorta as it passes through the diaphragmatic hiatus at the T12–L1 level. Major visceral branches include the celiac axis and the superior and inferior mesenteric arteries. The aorta terminates at L4, where it bifurcates into the common iliac arteries.

The celiac axis arises ventrally just caudal to the diaphragm. It supplies the liver, spleen, stomach, pancreas, and duodenum via the radicles of the left gastric, splenic, and common hepatic arteries. The superior mesenteric artery arises at the L1–L2 level and supplies the small bowel and colon from the ligament of Trietz to the splenic flexure. The left colon distal to the splenic flexure

Fig. 57–8. Mycotic aortic aneurysm at the junction of the descending thoracic and abdominal aortae. The side holes of the pigtail catheter are immediately adjacent to the aneurysm—the catheter should optimally be positioned more superiorly (see text).

is perfused by the inferior mesenteric artery, whose origin is usually at L3, slightly to the left of midline.

Visceral blood is returned via the portal venous system. The superior and inferior mesenteric, splenic, and left gastric veins converge in the upper abdomen to form the portal vein which courses obliquely upward to the right to enter the liver. Blood flows through the hepatic sinusoids into the hepatic veins and returns to the heart by way of the inferior vena cava.

Variations in visceral arterial anatomy are common, particularly in the blood supply to the liver. The right and left hepatic arteries are branches of the common hepatic artery in only half of the general population. The other half may have partial or total supply to the right lobe arising from the proximal superior mesenteric artery or the left hepatic artery originating from the left gastric artery.

Catheterization of the abdominal aorta and visceral arteries is most often performed for the investigation of hypertension, gastrointestinal bleeding, visceral masses, or transplants. In neonates, the examination may be accomplished by umbilical arterial catheterization; the transfemoral route is used after 2 weeks of age.

Abdominal Aortic Coarctation

Congenital fusiform narrowing of the abdominal aorta is proposed to result from abnormal fusion of the paired primitive dorsal aortae. Stenosis is most marked at the level of the renal arteries, and hypertension is a common presenting feature.

Hypoplasia of the abdominal aorta associated with renal and/or pulmonary artery stenoses may be seen in Williams[54] and con-

genital rubella[55] syndromes. In the former, mental retardation, "elfin facies," hypercalcemia, and supravalvular aortic stenosis are present. The syndrome is believed to be related to abnormal vitamin D metabolism. Babies suffering from the sequelae of prenatal rubella infection may have patent ductus arteriosus, ventricular septal defect, or other cardiovascular abnormalities.

Abdominal aortic coarctation is also a manifestation of Takayasu's arteritis (Fig. 57–9) and neurofibromatosis, both of which are discussed elsewhere in this chapter. Irradiation of abdominal or retroperitoneal neoplasms early in life, particularly in cases of Wilms' tumor, have resulted in a similar angiographic appearance.[56]

Liver Neoplasms

Hemangiomas and hemangioendotheliomas are benign hepatic neoplasms that classically present in the first year of life with cardiac failure, hepatic enlargement, and/or cutaneous hemangiomata.[57] Hepatic malignancies, including hepatoblastoma and hepatocellular carcinoma, are usually discovered in children who fail to thrive or who exhibit other nonspecific constitutional symptoms and have palpable hepatomegaly. Hepatoblastomas are found in the neonatal period, while hepatocellular carcinomas usually present after the fifth year; associated congestive heart failure is rare.[58,59]

Benign hepatic neoplasms are often differentiated from malignancies on the basis of clinical features and noninvasive diagnostic examinations.[60,61] Angiography is primarily used for presurgical vascular mapping or before embolotherapy. The presence of arteriovenous shunting, usually hepatic artery to hepatic vein, and sinusoidal pooling (Fig. 57–10) are distinctly more common in benign tumors, while segmental or main portal vein occlusion and arterial encasement are indicative of malignancy.[57,62] Marked hypervascularity may be seen in both groups.

Although histologically benign, hemangiomas and hemangioendotheliomas are sometimes associated with significant morbidity and mortality. Treatment has traditionally consisted of corticosteroids, radiation, or chemotherapy. Transcatheter embolization may be employed as a primary therapeutic modality or when the above options fail.[63]

Hepatoblastoma and hepatocellular carcinoma are usually surgically excised. If the neoplasm is unresectable, embolization may be offered in lieu of chemotherapy or radiation therapy.

Liver Transplant

Angiographic evaluation before and after liver transplantation has decreased in the past few years because of the refinement of Doppler ultrasonography and computed tomography.[64–67] Angiography is used to clarify abnormalities found during these studies or in cases in which noninvasive imaging is technically unsatisfactory.

The portal vein and inferior vena cava are evaluated preoperatively for patency and size. Most surgeons prefer the portal vein to be at least 4 to 5 mm in diameter before attempting transplantation.[68] Selective injection of the superior mesenteric or splenic arteries with filming carried into the venous phase will usually adequately visualize the portal vein (arterial or indirect portography). Direct injection into the inferior vena cava is performed via the percutaneous femoral venous approach.

Postoperatively, hepatic arterial abnormalities remain one of the most frequent causes of failed transplantation and may manifest angiographically as stenosis, thrombosis, or alternating foci of narrowing and dilatation indicative of rejection.[67,69] Abdominal aortography and/or selective hepatic angiography will detect these abnormalities; selective injection of the superior mesenteric artery should be added in cases of hepatic artery thrombosis, as collaterals to the liver have been reported in some patients.[69] This obviates the need for emergency retransplantation.

Portal Hypertension

Portal hypertension presents most commonly with upper gastrointestinal bleeding at 3 to 5 yr of age.[70] Hepatosplenomegaly and hypersplenism are often present at the time of diagnosis.

Gastroesophageal varices in children are most often formed on the basis of extrahepatic portal venous occlusion, which may occur congenitally (cavernous transformation) or develop postnatally secondary to umbilical venous catheterization, omphalitis, or sepsis.[62,71,72] Children with intrahepatic diseases, including biliary atresia, congenital hepatic fibrosis, cystic fibrosis, and viral hepatitis usually have jaundice or other stigmata of hepatic dysfunction before their first bleeding episode.[62]

Angiography and splenoportography are important in evaluating for sites of greatest collateral (hepatofugal) flow and thus in determining which decompressive shunt will be effective. Arterial portography, or opacification of the portal venous system following injection of the splenic and/or superior mesenteric arteries, provides information about venous anatomy and flow patterns. Splenoportography, or direct injection of contrast into the splenic pulp, provides superior anatomic detail of the venous drainage pathways (Fig. 57–11) at the risk of bleeding, particularly in children with clotting abnormalities related to liver dysfunction or hypersplenism. It is usually performed when arterial portography is inconclusive. Measurement of splenic pulp pressure, which mirrors hepatic sinusoidal pressure, is an added benefit of this method of examination.

Venous flow is typically bidirectional in extrahepatic obstruction, with hepatofugal flow through abdominal or retroperitoneal varices and hepatopetal flow through numerous worm-like veins in the liver hilus. In cases of intrahepatic disease, hepatopetal flow progressively decreases as hepatic sinusoidal pressure increases until total reversal of flow or thrombosis within the portal vein ensues. Collateral pathways visualized include esophagogastric, mesenteric, and periumbilical varices, as well as spontaneous splenorenal shunts.

The treatment of portal hypertension centers on the surgical creation of various portosystemic shunts.[70] Most surgeons prefer to defer operation until 5 yr of age, if possible, to allow the vessels to reach adequate size. Esophageal sclerotherapy and liver transplantation have played increasingly important roles in the management of these patients. Prognosis is considerably better in the extrahepatic forms of the disease, in which hepatopetal collaterals may enlarge over time and reduce flow through varices, sometimes eliminating the need for shunt surgery.

Gastrointestinal Bleeding

Gastrointestinal bleeding in children is most frequently related to esophagogastric varices as just discussed. Upper gastrointestinal bleeding of arteriocapillary origin may be from gastroduodenitis or ulceration. Sources of lower gastrointestinal bleeding include

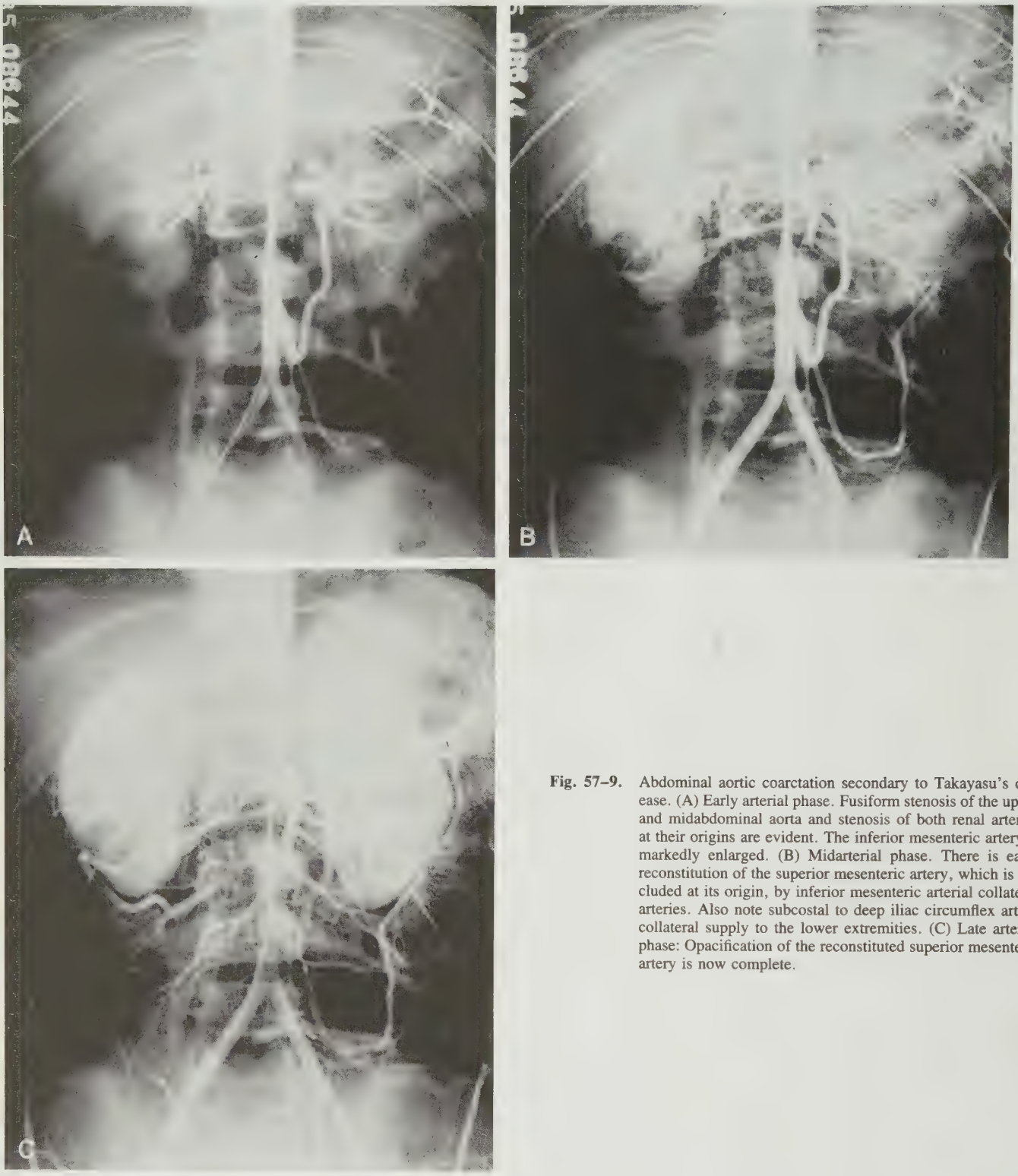

Fig. 57–9. Abdominal aortic coarctation secondary to Takayasu's disease. (A) Early arterial phase. Fusiform stenosis of the upper and midabdominal aorta and stenosis of both renal arteries at their origins are evident. The inferior mesenteric artery is markedly enlarged. (B) Midarterial phase. There is early reconstitution of the superior mesenteric artery, which is occluded at its origin, by inferior mesenteric arterial collateral arteries. Also note subcostal to deep iliac circumflex artery collateral supply to the lower extremities. (C) Late arterial phase: Opacification of the reconstituted superior mesenteric artery is now complete.

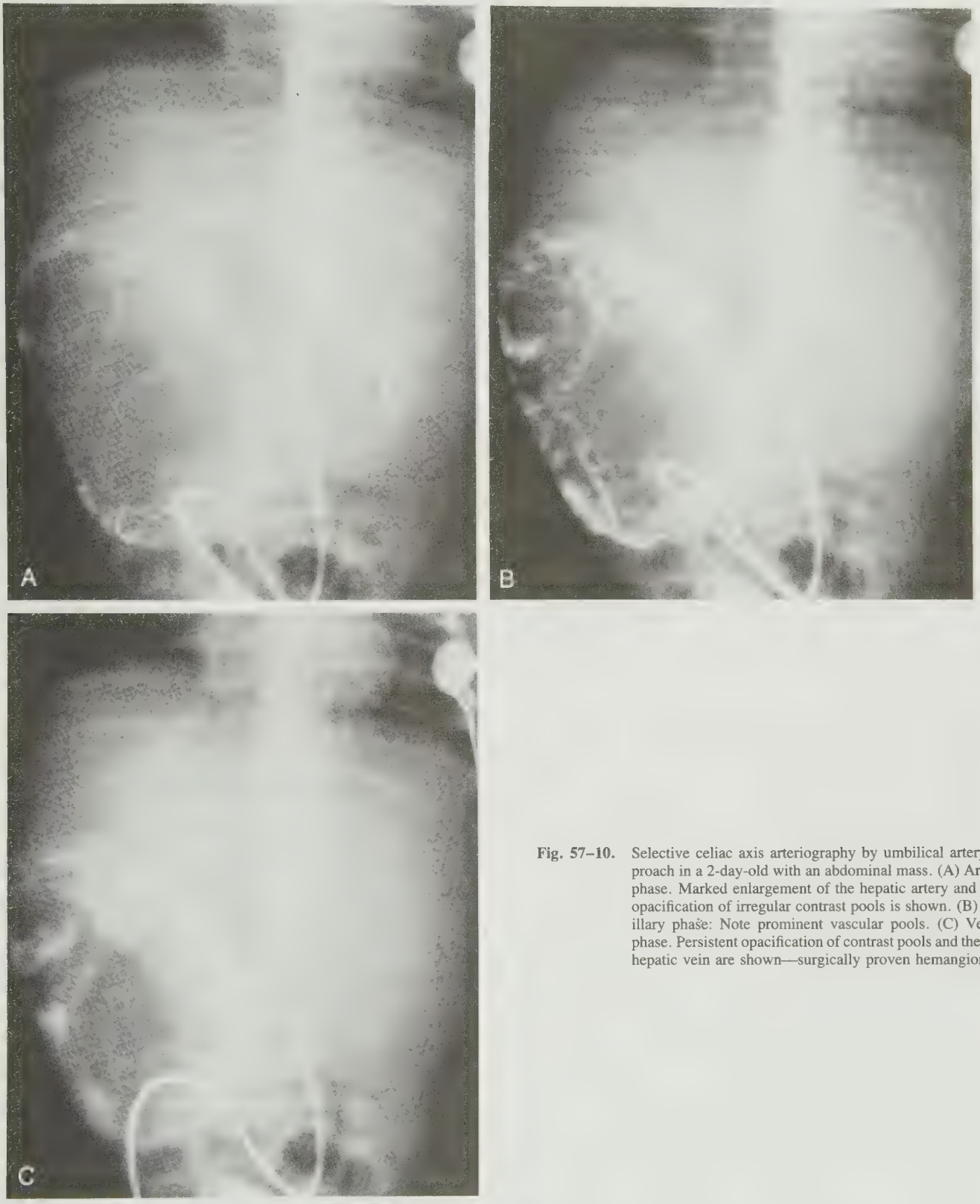

Fig. 57–10. Selective celiac axis arteriography by umbilical artery approach in a 2-day-old with an abdominal mass. (A) Arterial phase. Marked enlargement of the hepatic artery and early opacification of irregular contrast pools is shown. (B) Capillary phase: Note prominent vascular pools. (C) Venous phase. Persistent opacification of contrast pools and the right hepatic vein are shown—surgically proven hemangioma.

Fig. 57–11. Splenoportogram in a child with cavernous transformation of the portal vein. Two main channels comprise the portal vein in the hepatic hilus. Collateral flow through the left gastric vein (arrowhead), inferior mesenteric vein (large arrow), and a spontaneous splenorenal shunt (small arrow) are noted.

anal fissure, colitis, polyp, vascular malformation, typhlitis, and Meckel's diverticulum.[73–79] Aggressive diagnostic workup is indicated in cases of hemorrhage in which the source is not obvious clinically. Evaluation commences with appropriate endoscopic or nuclear medicine studies; barium is not administered before angiography in patients with moderate to severe hemorrhage, as it will obscure the mesenteric vasculature. Angiography is performed in patients with positive endoscopy or scintigraphy in whom further diagnostic information or transcatheter therapy is desirable.

A cobra-shaped or reverse-curve catheter is placed selectively in the celiac axis, left gastric, gastroduodenal, and/or superior mesenteric arteries in cases of upper gastrointestinal bleeding. The celiac axis and superior and inferior mesenteric arteries are injected when bleeding is believed to be from a lower gastrointestinal source. Intravenous vasopressin therapy should be terminated at the time of the study for the best chance of demonstrating active extravasation. Bleeding rates as low as 0.5 mL/min may be detected angiographically.[80] Findings include diffuse vascular spasm related to hypovolemia, contrast extravasation (Fig. 57–12), vascular malformation, and intense mucosal stain in cases of inflammation (e.g., colitis, gastritis, duodenitis). Arteriovenous shunting may be observed in malformations or inflammatory processes.

Transcatheter therapy in the form of vasopressin infusion or embolization have emerged as viable alternatives to the more traditional surgical approaches to gastrointestinal bleeding.[79,81] Vasopressin (Pitressin) may be administered into the left gastric, superior, or inferior mesenteric circulations in a dosage of 0.05 to 0.3 unit/min. After 15 min of infusion, a repeat angiogram is performed to confirm cessation of bleeding without excessive vasoconstriction, which could lead to bowel infarction. Embolization, generally with Gelfoam, is reserved for the left gastric artery. Caution is advisable when previous gastric or upper abdominal surgery has been performed as potential collateral pathways may have been severed. Occlusion of superior mesenteric and inferior mesenteric radicles should be avoided, as bowel infarction is likely.

Therapeutic Splenic Infarction

Hypersplenism related to congestive splenomegaly in a number of hematologic disorders (Banti's syndrome) has traditionally been treated by splenectomy. However, this procedure is associated with impairment of immunologic defenses and an increased incidence of overwhelming sepsis. Partial splenic embolization was proposed in an effort to preserve some splenic parenchyma and therefore immunologic integrity. Although initial efforts were marred by frequent complications, there has been renewed interest in the procedure after modifications, as set forth by Spigos et al. in 1979.[82] Their protocol calls for transcatheter ablation of two thirds of the splenic parenchyma with small Gelfoam pledgets soaked in antibiotics. Liberal use of parenteral antibiotics and narcotic analgesics for 5 days after the procedure has dramatically reduced postprocedural splenic abscess, sepsis, and hypostatic pneumonia.

Kumpe et al. reported successful partial splenic embolization in 10 of 11 children with biliary atresia and/or portal venous thrombosis.[83] Hypersplenism was corrected in 7 of 8 individuals and the frequency of variceal bleeding was reduced in all 10 patients. Reversal of leukopenia and thrombocytopenia secondary to hypersplenism in renal transplantation,[84] thalassemia,[85] and Gaucher's disease[86] has also been reported.

RENAL ANGIOGRAPHY

Catheterization for the investigation of renal abnormalities is the most frequently performed vascular examination in many pediatric radiology departments. Indications include evaluation for renal vascular hypertension, vasculitis, renal transplant donors and recipients, and less commonly, traumatic or neoplastic disease. The renal arteries usually are found at the L1–L2 level, although they may arise anywhere along the course of the distal abdominal aorta or common iliac arteries. The renal origins are optimally demonstrated in a slight right posterior oblique projection. Multiple arteries are present in up to 35% of normally positioned kidneys and in the majority of ectopic and horseshoe kidneys.[87]

The segmental veins converge at the renal hilus to form the main renal veins, which course cranially to join the inferior vena cava at the L1–L2 level. The most common venous variant is a circumaortic left renal vein in which dorsal and ventral components of a venous collar around the aorta are found. Its recognition is important when performing renin sampling or in evaluation of renal donors. Venous anatomy is extremely variable in ectopic and horseshoe kidneys.

Selective renal arteriography should always be preceded by midstream abdominal aortography so that spasm induced by the catheter is not mistaken for a focus of fixed pathologic narrowing and so that the number of arteries to each kidney is determined. Aor-

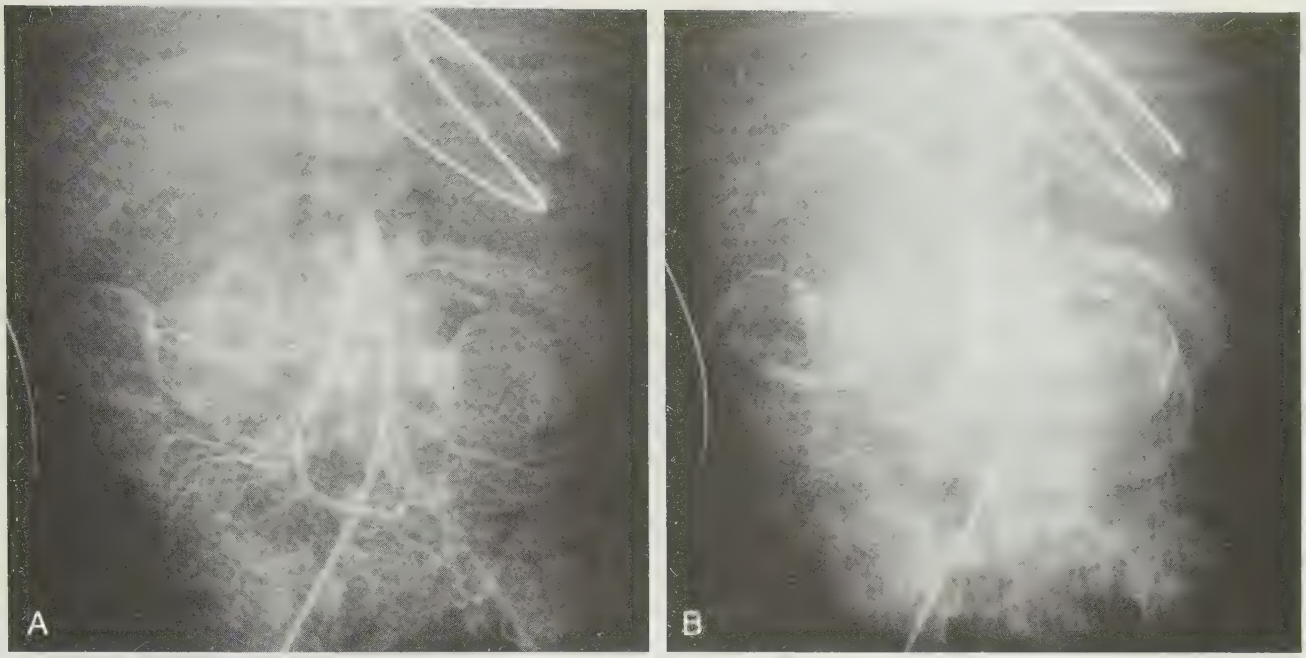

Fig. 57–12. Acute gastrointestinal hemorrhage. Arterial (A) and venous (B) phases of a selective superior mesenteric arteriogram. Contrast extravasation is seen to the left of L2 secondary to an ulcer in the proximal jejunum.

tography is performed with a No. 4 or No. 5 French pigtail catheter; a simple, reverse-curve or cobra catheter is suitable for selective injection.

Renal Vascular Hypertension

Hypertension is uncommon in the pediatric age group, affecting only 1 to 2% of this population.[88] High blood pressure may be discovered incidentally during an office visit or may present with nonspecific symptoms of headache, visual disturbances, nausea, or vomiting.[89,90] Sustained diastolic pressure of greater than 90 mm Hg is generally considered elevated in older children; pressures standardized for height and weight are available for younger children.[91]

Patients discovered fortuitously to have elevated pressure do not necessarily require extensive workups for renal vascular disease unless they are under 10 yr of age. A noninvasive evaluation consisting of urinalysis, complete blood count, determination of serum levels of blood urea nitrogen and creatinine, and ultrasound for kidney size is recommended in these patients.[89] If, however, there is an audible bruit, acceleration of hypertension, or if control of blood pressure is refractory to medical therapy, angiography should be performed. My colleagues and I also routinely perform angiography in patients under 10 yr old with hypertension; in fact, the younger the child, the more likely a renal vascular cause will be found.[92]

For children who present with nonspecific symptoms, a noninvasive evaluation as described above is followed by a percutaneous biopsy if the urinalysis, blood urea nitrogen, and creatinine suggest renal parenchymal disease. If these parameters are normal, angiographic evaluation is undertaken. In the series of Londe, 78% of patients had parenchymal disease to account for their hypertension, 12% had renovascular causes, and the remainder had miscellaneous abnormalities.[89]

Angiography is preceded by bilateral selective renal vein renin samples, which are obtained via a femoral venous approach. A cobra-shaped catheter is usually most effective; the catheter tip should be advanced distal to the gonadal vein orifice on the left side for accurate sampling. Samples are also taken from the inferior vena cava above and below the level of the renal veins. Arterial DSA is helpful in localizing veins in cases of ectopic and horseshoe kidneys, in which anomalous drainage pathways are common. A detailed discussion of renin interpretation may be found elsewhere;[93,94] however, a renin ratio of greater than 1.5 from one kidney to the other suggests a significant parenchymal or vascular lesion.

Abdominal aortography and selective injection of both renal arteries are then performed; the latter should be done for a complete examination. The most frequent cause of renal vascular hypertension is fibromuscular dysplasia.[93–97] Lesions may be focal, web-like or broad, smooth stenoses, unlike the classic "string of beads" found in adults. The distal two thirds of the main renal artery and segmental arteries are most commonly affected; the adjacent aorta is normal.

When tubular narrowing of the abdominal aorta is observed in association with compromise of the renal arteries, Takayasu's disease, neurofibromatosis, and other causes of abdominal aortic coarctation are the main differential considerations.[26–28,54–56,97–99] As previously discussed, the renal arteries are involved in up to 75% of cases of Takayasu's disease. Angiographically, stenoses are found at the ostium and proximal one third of the renal artery; poststenotic aneurysm formation is not uncommon. Although both Takayasu's disease and neurofibromatosis may produce identical angiographic pictures, they are usually easily distinguished on clinical grounds. When stenosis of neurofibromatosis uncommonly occurs in the distal two thirds of the renal artery, differentiation from fibromuscular dysplasia is difficult (Fig. 57–13).

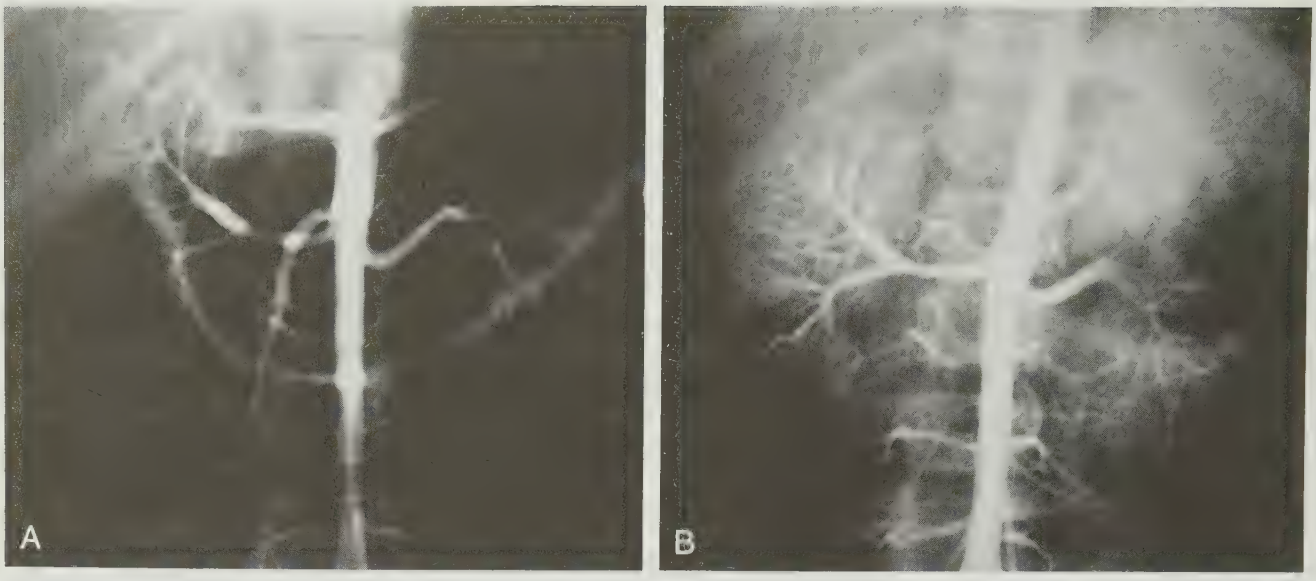

Fig. 57–13. Renal artery stenosis in a young boy with neurofibromatosis and hypertension. (A) High-grade focal stenosis of the distal right renal artery with poststenotic dilatation extending into the upper pole segmental artery. Neurofibromatosis more commonly affects the renal artery ostia, although it may compromise the distal vessel. The appearance of this lesion is indistinguishable from fibromuscular dysplasia. (B) The same view after transluminal angioplasty, with excellent results.

Hypertension is also known to be associated with placement of umbilical arterial catheters in the neonatal period.[100–102] In the short term, evidence of thromboemboli to the main or segmental renal arteries is observed. In later years, angiography may reveal renal infarcts or a globally small renal artery and kidney indistinguishable from other causes of hypoplasia or atrophy. Hypertension is also a common feature of vasculitis, which is discussed in the next section.

After the discovery of a renal stenosis, transluminal angioplasty may be attempted. A vascular surgeon must always be immediately available in case there are complications. Antihypertensive medication should be discontinued to avoid postprocedural hypotension. The narrowed segment is first traversed by a tapered soft-tipped straight guide wire such as a Bentson guide wire (Cook Co., Bloomington, IN), over which a catheter is advanced into the distal renal artery. A reverse-curve shape is the most effective in crossing tight stenoses. Heparin is routinely administered through the catheter in a dose of 50 to 100 units/kg; spasm may be relieved at any time during the procedure by intra-arterial nitroglycerin. A more rigid wire (i.e., Rosen, Bard Inc., Billerica, MA) is then placed into the distal renal artery, followed by the double-lumen balloon catheter. Balloon size should be equal to the luminal diameter of the normal renal artery just distal to the stenosis as measured on conventional angiographic films; care should be taken not to choose a site of poststenotic dilatation for the measurement. With the balloon centered on the lesion, one or more inflations for 30 sec to 1 min are made until the "waist" has been eliminated. The wire is removed and pressure tracings and readings are obtained to ensure a good result with no residual gradient. My colleagues and I usually perform arterial DSA of the abdominal aorta to angiographically document the results.

Increasing numbers of series in the literature document the utility and success of renal dilatation.[103–108] Angioplasty has been recognized as the treatment of choice for renal vascular hypertension secondary to fibromuscular dysplasia and is curative in the majority of these patients.[109] Although initial reports of dilatation in Takayasu's disease and neurofibromatosis were less than optimal,[110] recent reports are more encouraging. Dong et al. report cure or marked improvement in 22 hypertensive patients followed an average of 25.5 mo after renal angioplasty.[111] However, Mali et al. suggest that lesions occurring within the proximal third of the artery are less responsive to dilatation.[103]

Vasculitis

Polyarteritis nodosa is a systemic necrotizing vasculitis that is probably related to immune complex deposition in medium and small vessels. The pulmonary arteries are spared; any other artery in the body may be affected. Clinical findings include fever, weight loss, hypertension, abdominal pain, and peripheral or central nervous system symptomatology.[112] There are no set criteria for the diagnosis of polyarteritis. Presumptive diagnosis is established by histologic evidence of necrotizing vasculitis or typical angiographic features in the proper clinical setting.

Abdominal aortography and selective visceral injections classically reveal aneurysms 1 to 5 mm in diameter in the hepatic, splenic, renal, and mesenteric vasculature. The series of Sellar et al. suggests that aneurysms are found only during periods of florid activity[113]; regression has been documented with appropriate medical therapy and coincides with clinical improvement.[114,115] Abnormal vessel tapering with areas of fusiform dilatation, occlusion, and visceral infarctions may be observed (Fig. 57–14). These angiographic features alone are indistinguishable from other causes of necrotizing angiitis and hypersensitivity, including amphetamine abuse, collagen vascular disease, and particularly, systemic lupus erythematosus.

Glucocorticosteroids and cytotoxic drug therapy have been reported to improve the 5-year survival rate to about 80%. Approx-

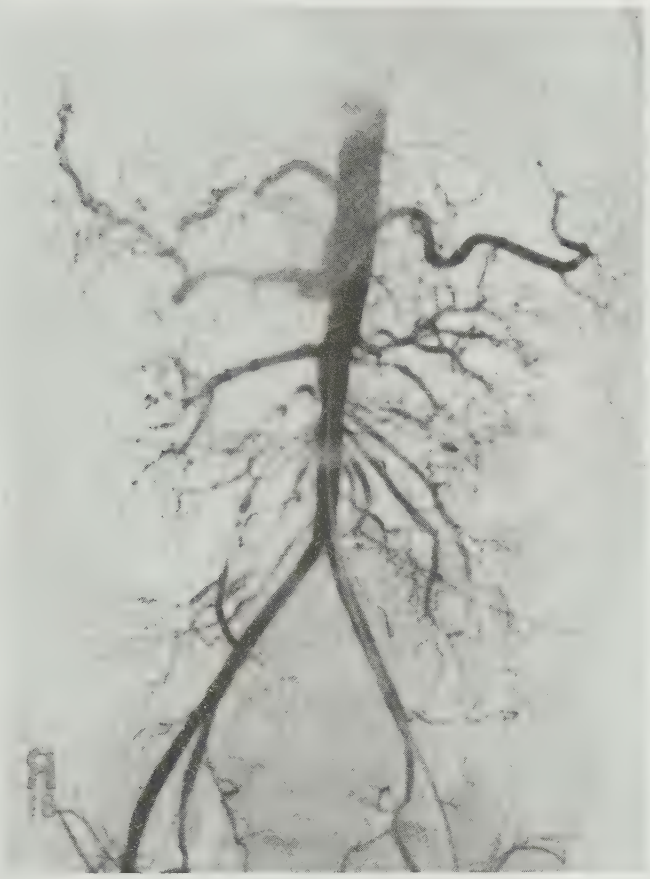

Fig. 57–14. Midstream abdominal aortogram in a young girl with clinically suspected polyarteritis nodosa. There is irregular tapering of numerous small and medium-sized mesenteric, visceral, and pelvic arteries with alternating foci of narrowing and dilatation. Marked spasm of the left external iliac artery is seen about the catheter. The patient's pedal pulses returned shortly after removal of the catheter.

imately 50% of patients eventually die from renal complications of their disease.[30]

Renal Donor and Transplant Evaluation

Angiography is performed in prospective renal donors to assess the number of renal arteries, length of the undivided main renal artery, and unsuspected arterial or venous abnormalities.[116] Arterial DSA of the abdominal aorta via the femoral artery approach is done on an outpatient basis. Filming is in the anteroposterior projection and supplemented with oblique views as necessary. Conventional film angiography and selective renal injections are rarely needed.

After transplantation, deteriorating renal function and hypertension may be related to vascular compromise as well as a number of parenchymal problems. Noninvasive imaging with Doppler ultrasound is quite helpful in the evaluation for vascular integrity.[117] Patients with equivocal results on Doppler study or evidence of a hemodynamically significant stenosis undergo subsequent angiography.

Selective injection of the common iliac artery ipsilateral to the transplant in a steep posterior oblique or lateral projection is usually necessary to demonstrate the arterial anastomosis. Filming is extended through the capillary and venous phases.

Stenosis may occur at or just distal to the anastomosis and range from very focal to smoothly tapering types (Fig. 57–15).[118] Poststenotic dilatation or arterial occlusion may also be observed. Percutaneous transluminal angioplasty has been effective in the nonsurgical management of these patients.[119–121] Retrograde puncture of the ipsilateral common femoral artery is the preferred approach to most lesions. High-pressure balloons are sometimes needed for resistant stenoses related to fibrosis.

If hypertension and renal insufficiency are performed on the basis of transplant rejection, irregular tapering and occlusion of segmental and more peripheral radicles with decreased arborization is observed. Slow flow and a patchy capillary phase are the result of an overall increase in vascular resistance through the transplant.

Renal Trauma

Renal injury is a result of blunt, penetrating, or iatrogenic trauma. Hematuria is the most common presenting feature, although its absence does not preclude a serious vascular or parenchymal insult. Indications for renal angiography include hematuria, hypotension following flank trauma, nonvisualized kidney on IVP, or absence of perfusion on computed tomography. Occlusion, arteriovenous fistula, extravasation, aneurysm formation, renal fracture, and subcapsular or perirenal hematoma can be demonstrated angiographically; arteriovenous fistula may result from renal biopsy.[122]

Transcatheter embolization may be performed in individuals in whom there is clinical evidence of persistent hemorrhage. The catheter is advanced peripherally in close proximity to the lesion in an effort to preserve a maximum amount of renal parenchyma.

Fig. 57–15. Arterial DSA demonstrating a tight anastomotic stenosis of a left iliac fossa renal transplant in a 2-yr-old boy.

Small Gelfoam pledgets are most often employed for occlusion in these circumstances.

Renal Neoplasm

Wilms' tumor is the most common solid abdominal tumor of childhood, and is usually discovered in the first 6 years of life. Children may present with an abdominal mass, pain, or hypertension. The major objectives in the initial staging efforts are determination of local extension, venous invasion, and distant metastasis. Ultrasound and computed tomography have all but eliminated the need for preoperative angiography because of their ability to accomplish these goals noninvasively.[123]

The utility of angiography is in its ability to delineate arterial and venous anatomy, particularly in large neoplasms before resection, and in determining the feasibility of limited resection in cases of bilateral tumors.[124] More than 90% of cases are hypervascular with typical tumor vessels (irregular tapering, abrupt angulations, unpredictable course) (Fig. 57–16). Aneurysms and arteriovenous shunting may be observed. Avascular foci within the mass usually represent necrosis. Preoperative embolization of these neoplasms has been reported.[125]

PELVIS AND EXTREMITIES

The vascular supply to the pelvis and lower extremities is schematically represented in Figure 57–17. The internal iliac arteries are important sources of collateral blood supply to the lower extremities and give rise to posterior (superior gluteal) and anterior (inferior gluteal, obturator, and internal pudendal) division radicles. These vessels have rich anastomoses with the iliac and femoral circumflex arteries caudally, and send branches across the midline of the pelvis. Other important collateral pathways not shown in the diagram include internal mammary to inferior epigastric and superior to middle and inferior hemorrhoidal arteries.

The profunda femoris artery is an important vessel in circumventing occlusions of the superficial femoral artery via its muscular branches. The superficial femoral artery becomes the popliteal artery as it exits the adductor canal in the lower thigh; the latter gives rise to the peroneal, anterior, and posterior tibial arteries, which serve as the distal "runoff" vessels.

The most common variations in pelvic arterial anatomy involve the anterior division branches of the internal iliac arteries. It is often possible to ascertain their origins only by tracing them retrogradely from their more constant distal ramifications. The branches of the popliteal artery are also quite variable; the anterior tibial artery frequently arises above the knee joint.

An uncommon anomaly is persistence of the embryologic sciatic artery. During early development, this enlarged continuation of the inferior gluteal artery serves as the axial vessel to the lower extremity. When regression fails to occur, its aberrant course posterior to the hip joint predisposes it to chronic trauma with subsequent occlusion or aneurysm formation. A lateral arteriogram of the pelvis is diagnostic.

The vasculature to the upper extremity is as illustrated in Figure 57–18. The axillary artery is the direct continuation of the subclavian artery distal to the first rib. The axillary artery becomes the brachial artery at the level of the anatomical neck of the humerus; the latter gives rise to the radial, ulnar, and interosseous arteries in the forearm.

A rich collateral vascular network is present about the shoulder joint, which is beyond the scope of this discussion. Collateral circulation about an occluded brachial artery at the level of the elbow joint is provided primarily by the superior and inferior ulnar collateral, deep brachial and radial, ulnar, and interosseous recurrent arteries.

The most common variants in the arterial supply to the arm involve the origin of the radial or ulnar arteries from the axillary or proximal brachial vessels. Persistence of the median artery, an embryologic vessel, is analogous to persistence of the sciatic artery in the legs. Associated absence of the radial and/or ulnar arteries may be found.

The pelvis and lower extremities can be imaged on a single film in the neonate and young infant. However, radiologic examination in older children and adolescents requires specialized equipment. Stepping tables move incrementally to follow the contrast as it flows distally; films are exposed at appropriate preset intervals. Long film changers image the entire extremity on 14-by-51-in. cassettes while the table remains stationary. Neither stepping tables nor long film changers are used in upper extremity angiography. Multiple runs are usually required to cover the entire arm, since the field that can be imaged on each injection is limited by the size of the image intensifier in the case of DSA or the film changer for conventional studies.

Visualization of the peripheral upper- and lower-extremity vasculature in infants and children is frequently limited by spasm. Intra-arterial injection of vasodilators, including tolazoline (Priscoline) or nitroglycerin will offer enhanced visualization of these vessels. Caution is advised when instilling these agents into the upper extremities, as reflux into the vertebral or carotid arteries may result. After administration of these agents, injection rates are increased 25 to 50% to compensate for the increased flow.

Congenital Abnormalities

Vascular malformations comprise the majority of congenital abnormalities of the pelvis and extremities and will be discussed in Chapter 85. Popliteal artery entrapment syndrome is a rare congenital cause of lower-extremity vascular insufficiency related to an abnormal course of the popliteal artery or adjacent muscular attachments. There is a male preponderance (8:1) and bilateral involvement in 20% of cases.[126] Angiographic features are medial or, less commonly, lateral deviation and narrowing of the midportion of the popliteal artery; popliteal artery thrombosis; or aneurysm formation (Fig. 57–19). Characteristic findings may be elicited by passive plantar flexion of the foot if not apparent on neutral position arteriography. Treatment is surgical and is usually curative.

Trauma

Iatrogenic iliofemoral arterial trauma secondary to diagnostic or therapeutic catheterization may result in acute ischemia or chronic sequelae, including limb-length discrepancy. There is considerable controversy regarding the frequency at which limb shortening develops as a result of catheterization.[18–20] Most authors feel that uncomplicated transfemoral percutaneous catheterization in children does not impair the blood flow to the limbs. However, there appears to be a relation between documented thrombosis and subsequent limb-length discrepancy. The younger the age at which thrombosis occurs, the greater the growth retardation appears to

Fig. 57–16. Wilms' tumor. (A) Selective renal artery injection reveals typical neovascularity. (B) Capillary phase. (C) Inferior venacavogram showing tumor thrombus protruding from left renal vein into the inferior vena cava.

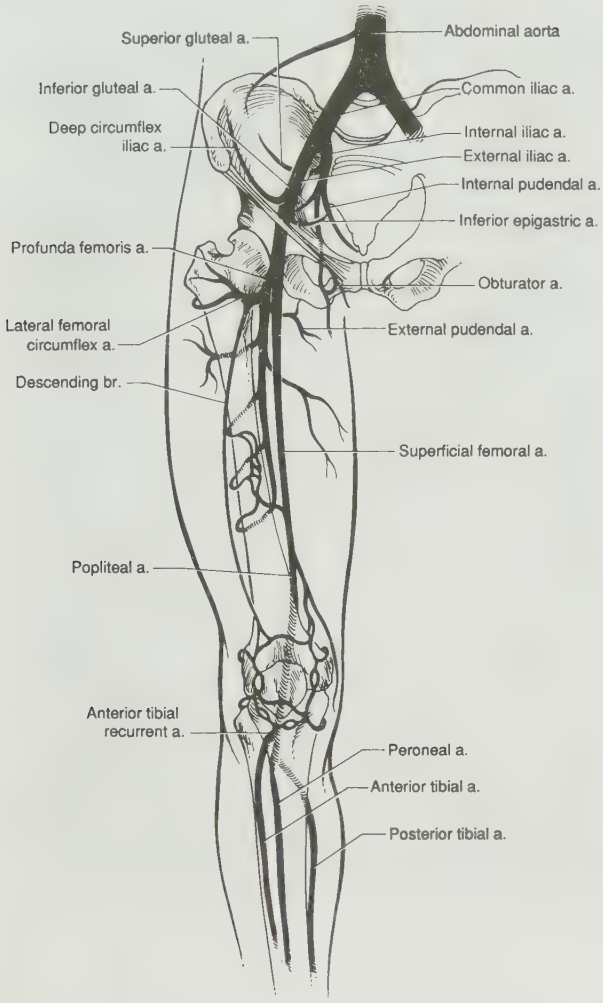

Fig. 57–17. The vascular supply to the pelvis and lower extremities. a. = artery; br. = branch.

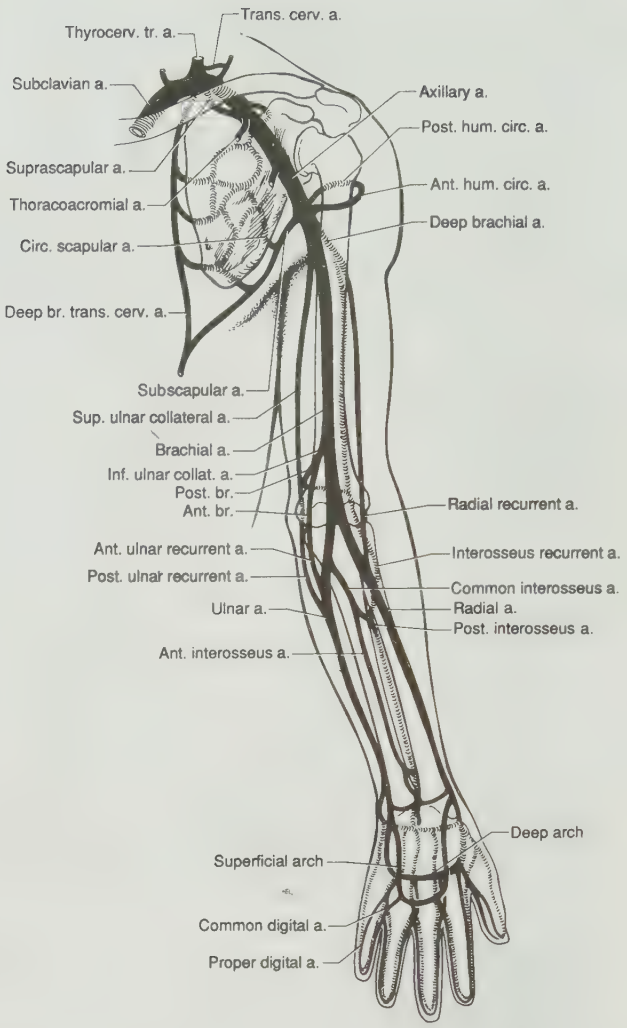

Fig. 57–18. The vasculature to the upper extremity. a = artery; br. = branch; Inf. = inferior.

be.[19] A higher incidence of postprocedural thrombosis is found in children who have undergone surgical arteriotomy for vascular access as compared with percutaneous catheterization by the Seldinger technique.[19]

Immediately after the trauma, angiography reveals intraluminal thrombus, dissection, occlusion, or spasm. Examination of the entire lower extremity is appropriate to rule out distal embolization. Chronically, stenosis or occlusion is found (Fig. 57–20). Collateral blood flow from the internal iliac arteries is generally well established. Investigation in these cases is via retrograde puncture of the contralateral femoral artery and injection of contrast at the aortic bifurcation.

Angiographic evaluation of the pelvis and extremities after severe blunt or penetrating trauma is performed to optimize surgical treatment or before performance of transcatheter embolization. Crush and penetrating injuries of the pelvis should be studied as early as clinically feasible.[127]

Indications for emergency angiography after extremity trauma are pulsatile bleeding, expanding hematoma, decreased or absent peripheral pulses, distal ischemia, bruit, or neurologic deficit.[128,129] The frequent association of vascular injury with supracondylar

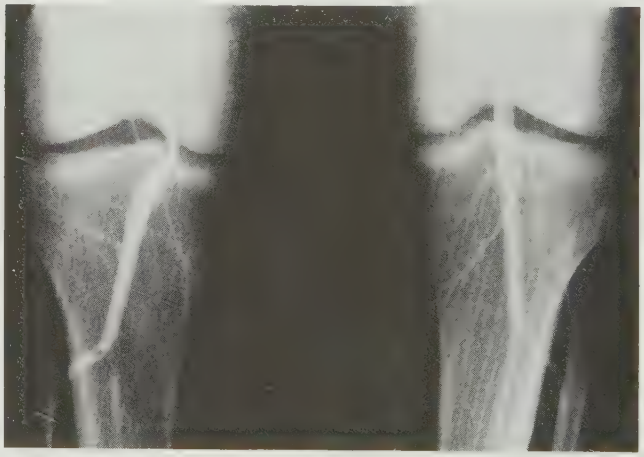

Fig. 57–19. Popliteal artery entrapment syndrome with aneurysm formation and subsequent embolization to the trifurcation vessels on the right side. The left popliteal artery appears normal.

Fig. 57–20. Fusiform stenosis throughout the course of the left external iliac artery related to prior catheterization. The child had a mild limb-length discrepancy. Note the enlargement of the left internal iliac artery, which serves as the main source of collateral supply to the left leg.

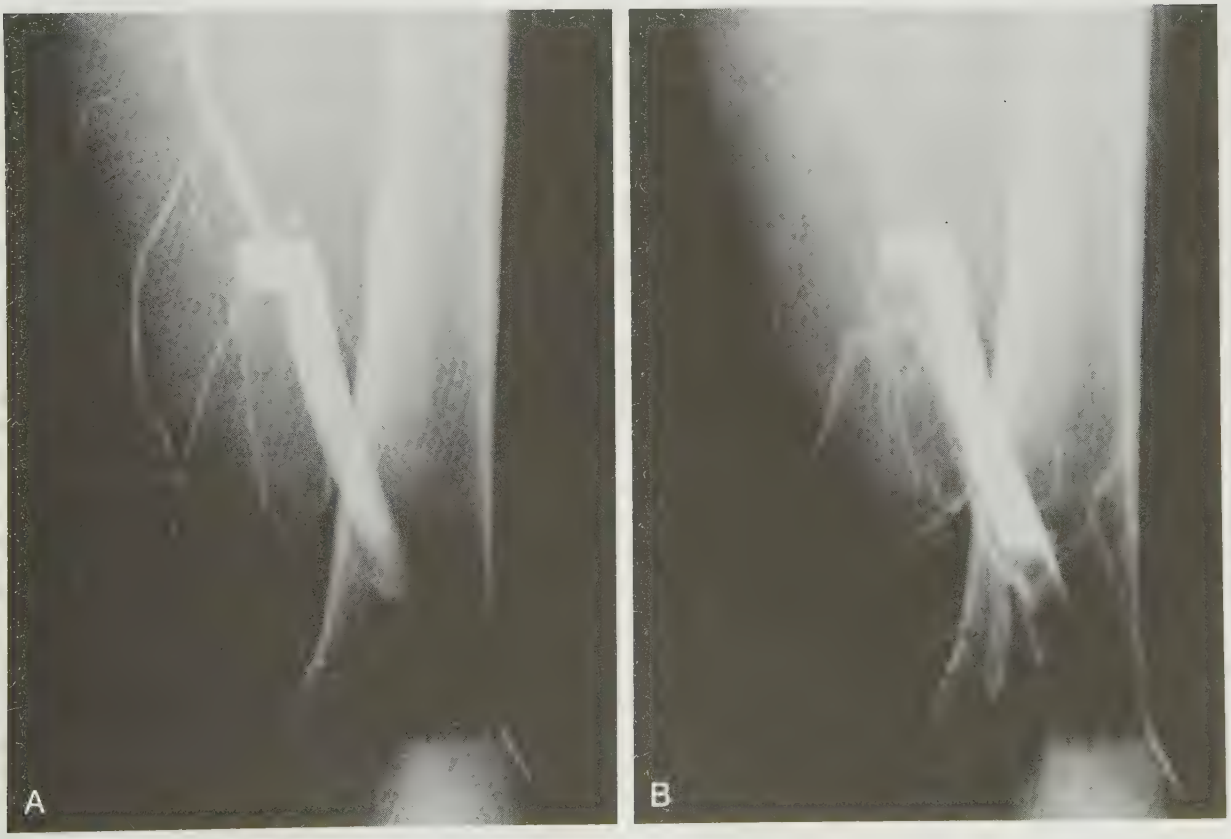

Fig. 57–21. Traumatic arteriovenous fistula between superficial femoral artery and femoral vein secondary to a stab injury. (A) Early phase. (B) Late phase. Note the thrombus within the femoral vein and poor filling of the proximal popliteal artery with abrupt termination (arrows), also secondary to intraluminal thrombus, proven surgically.

fractures of the humerus and femur warrants routine angiographic assessment. Penetrating trauma in the proximity of a major vessel may be studied electively if clinical signs do not suggest vascular compromise.

Vascular studies may disclose extravasation, thrombosis, arteriovenous fistula (Fig. 57–21), pseudoaneurysm, intimal flap, or fusiform narrowing related to spasm or hematoma. Distal aortic and subsequent selective internal iliac arteriograms are quite sensitive in detecting extravasation in the pelvis; arterial DSA or conventional film studies may be obtained. Investigation of trauma to the extremities should be performed in a second projection for clarification of an abnormality or if an abnormality is not disclosed on the first injection. Actively bleeding internal iliac arterial radicles or muscular branches in the extremities that are deemed to be clinically significant at the time of angiography may be embolized with small Gelfoam pledgets.[130,131]

Risks of transcatheter occlusion include errant placement of embolic material, muscular or skin necrosis, and ischemia to the sciatic nerve.[132]

Neoplasm

Plain films, ultrasound, computed tomography, and/or magnetic resonance imaging are integral and complementary examinations in the diagnostic evaluation of pelvic and extremity neoplasms. Angiography is not commonly performed for diagnostic purposes, although it is a necessary prelude to transcatheter embolization or infusion.

Preoperative embolization of benign vascular osseous neoplasms including aneurysmal bone cyst, osteoblastoma, and giant-cell tumor is helpful in limiting hemorrhage related to resection or curettage of these lesions.[133] In surgically inaccessible regions such as the lower lumbar vertebrae or pelvis, this procedure may serve as the primary mode of therapy.

Intra-arterial chemotherapy for osteosarcoma permits high drug concentrations to be delivered to a localized neoplasm. Encouraging results after infusion of doxorubicin (Adriamycin) or cisplatin (*cis*-diamminedichloroplatinum II) for potential limb salvage and as an adjunct to radiation therapy in surgically inaccessible regions have been achieved.[134]

Dialysis Access Evaluation

Internal dialysis access is achieved by creation of an arteriovenous anastomosis or graft. The Brescia–Cimino internal fistula is an arteriovenous anastomosis between the radial artery and cephalic vein in a side-to-side fashion within the forearm. Occasionally, the distal ulnar artery and an adjacent vein are used. An arteriovenous graft is constructed with synthetic material, usually expanded polytetrafluoroethylene, in a U-shaped subcutaneous tunnel within the proximal forearm between the brachial artery and antecubital vein.[135]

Access failure may be related to thrombosis, arterial or venous stenosis, or infection. Thrombosis and infection are usually evident clinically and do not require radiographic evaluation. Arterial stenosis will present as reduced inflow into the uptake dialysis catheter or peripheral ischemia. Venous stenosis, which is more common, is manifest as distal varicosities, upper extremity edema, increased venous perfusion pressure, and pain at the fistula site. Poor filtering may occur as a result of preferential recirculation to the arterial side of the fistula rather than anterograde flow through the stenosis.

Fig. 57–22. Venous stenosis proximal to an arteriovenous interposition graft in the forearm (adjacent to metallic clips).

Fistulography is performed as described by Gilula et al.[136] An 18- or 20-gauge butterfly needle is placed into the venous side of the fistula or anastomosis. A blood pressure cuff is inflated on the upper arm to above systemic arterial pressure, and 15 to 25 mL of low-osmolarity contrast material is injected at approximately 3 to 4 mL/sec. Contrast material will flow both anterogradely through the venous side as well as retrogradely to the arterial side. The cuff is then deflated to observe washout. Visualization of the venous system centrally to the superior vena cava is recommended as stenosis remote from the access site is possible (Fig. 57–22).

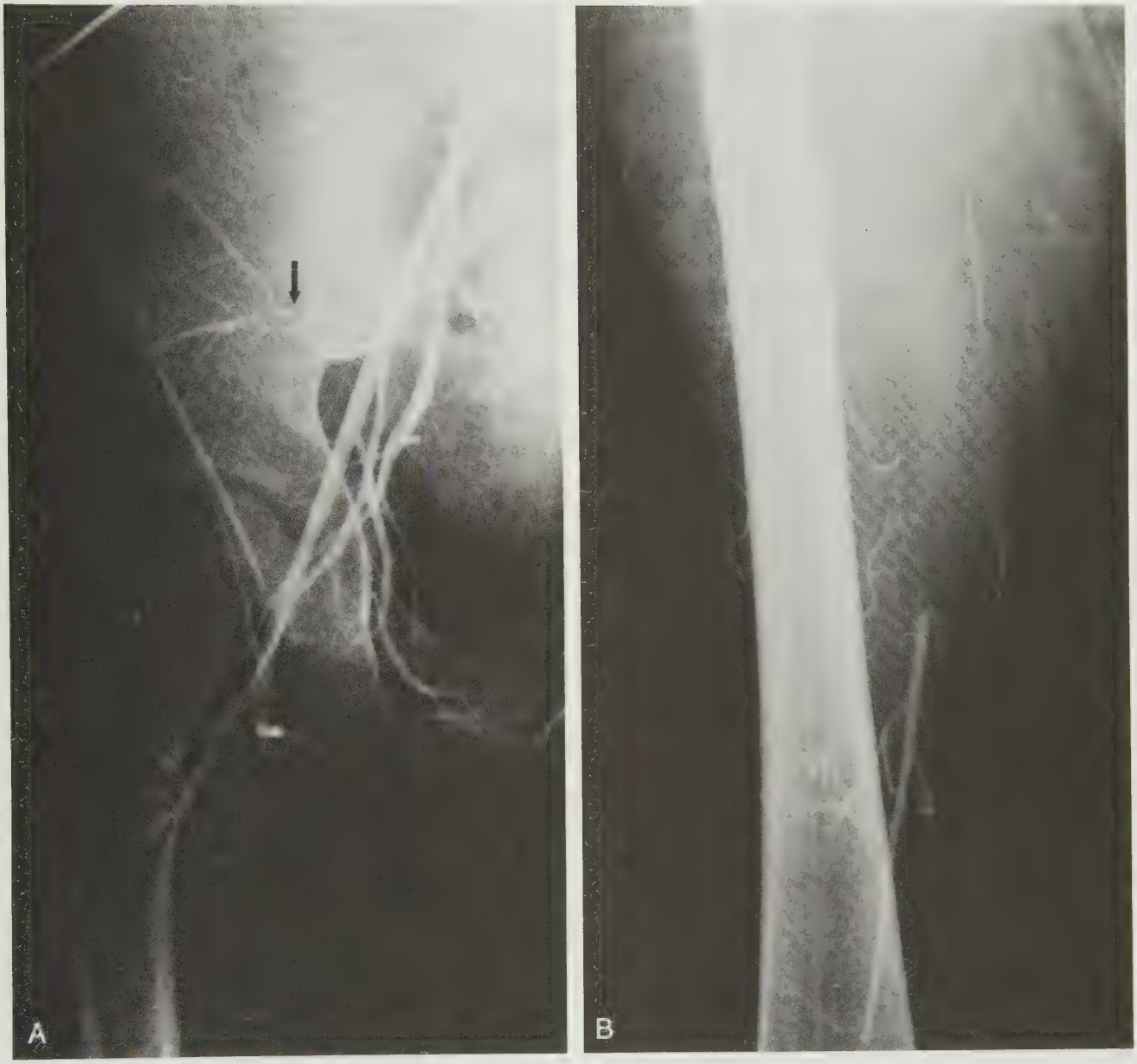

Fig. 57–23. Multiple emboli to the internal iliac (arrow), profunda femoris (A) and superficial femoral (B) arteries secondary to subacute bacterial endocarditis.

Pseudoaneurysms of the arteriovenous anastomosis or graft are commonly observed, and are related to dialysis trauma.

Transluminal angioplasty of dialysis access stenosis has been reported by several authors.[135,137–139] The procedure is best attempted via direct puncture of the venous side of the anastomosis and subsequent anterograde or retrograde passage of the catheter through the site of narrowing. Balloon sizes are generally chosen to be 1 mm larger than the expected normal luminal caliber. High-pressure balloons are often necessary to eliminate pressure gradients across stenotic foci related to dense fibrosis.

MISCELLANEOUS DISORDERS

As previously discussed, emboli to the peripheral vasculature may be secondary to umbilical artery catheters used in the neonatal period. In later childhood and adolescence, friable valvular vegetations of bacterial endocarditis are the most common source of peripheral emboli (Fig. 57–23). Emboli related to an aneurysm or tumor are rare.

Peripheral arterial aneurysms are most frequently posttraumatic, although they have been described in Ehlers–Danlos syndrome, polyarteritis nodosa,[140] Kawasaki disease, and fibromuscular hyperplasia. Mycotic aneurysms more commonly involve the aorta, though infrequently they occur peripherally.

Angiographic evidence of peripheral arteritis, namely contour irregularity with abnormal tapering, may be seen in the necrotizing vasculitides of which polyarteritis nodosa is the prototype. This entity is covered in the discussion on renal angiography.

Vasospastic disorders such as Raynaud's disease are associated

with spasm and occlusive changes in the medium and small vessels of the extremities. When found in association with an underlying disorder such as rheumatoid arthritis or systemic lupus erythematosus, it is referred to as Raynaud's phenomenon. A triphasic disorder consisting of initial vasoconstriction (digital pallor) followed by relaxation of the capillaries and venules (cyanosis) and reactive hyperemia (rubor) is clinically observed. This sequence is initiated by cold or emotional stimuli. Angiographically, proximal vessels are normal; distally, intense spasm or occlusion of medium-sized and small vessels is present.

THE FUTURE

One of the most promising vascular imaging methods to be developed in recent years is magnetic resonance imaging (MRI). The high inherent contrast between the arterial lumen and surrounding soft tissue lends itself to the generation of an MRI "angiogram" when a thick-slice technique is used.[141] Resolution, expense, and time requirements are presently suboptimal, although they will improve as new techniques such as narrow flip-angle excitation with gradient refocusing are used.[142] Examination of the aorta and its major branches with MRI is now possible; further refinements are expected to obviate and/or complement angiography in imaging smaller and more peripheral arteries.

Expandable metallic vascular stents designed by Gianturco[143] and Palmaz[144] are being evaluated for use in both arteries and veins. Rather large introducing sheaths are required for their placement, which may limit their application in infants. In older children, these stents will likely have a favorable impact in the therapy of pulmonary, aortic, and branch-vessel stenoses, particularly in Takayasu's disease and neurofibromatosis.

Introduction of low-osmolarity contrast agents into clinical practice has been received with great enthusiasm. Ongoing research in this field will undoubtedly result in the approval of newer solutions that are iso-osmolar to plasma, without sacrificing iodine content. It is hoped that this may be achieved at a substantial reduction in cost and result in a safer agent. Iotrolan, a high-molecular-weight nonionic dimer, is one of several such compounds currently undergoing clinical trials in Europe.[8]

Finally, it is well known that local complications at the puncture site may be minimized by using the smallest possible catheter. A minipuncture catheterization technique has been recently described by Cope et al.,[145] which may be helpful in achieving this end. Double-lumen angioplasty catheters with smaller shafts are being developed; balloons up to 8 mm in diameter on 5 French shafts have recently been introduced (Medi-Tech, Inc., Watertown, MA) and will perhaps become even more streamlined for less traumatic introduction into the vascular system in future years.

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UNIT 4

STRUCTURAL CONGENITAL CARDIOVASCULAR DEFECTS

CHAPTER 58

Clinical Physiology of Left-to-Right Shunts

Madeline S Mas
J Timothy Bricker

The purpose of the four clinical physiology chapters of this text (Chapters 58, 62, 70, and 76) is to provide a brief overview for the beginning student of congenital heart disease. It is expected that these chapters, written at the level of the pediatric resident, will supply some introductory concepts and serve as a framework for the concepts and references discussed in greater detail in the chapters of the book that follow. It is also hoped that these four brief chapters might help the more experienced trainee in pediatric cardiology solidify concepts important in patient management.

Although there are limitations inherent in the reduction of complex physiology to simple prototypes, this is often helpful in the attempt to ascertain the physiologic importance of a cardiac defect in a specific patient. There is a seemingly infinite number of rare variants of complicated types of malformations, but it is relatively easy to reduce the defects to those with one of five types of physiology: left-to-right shunts, right-to-left shunts, transposition physiology, obstructive lesions, and regurgitant lesions. Thus, the patient with a single ventricle who does not have pulmonary stenosis can be understood in consideration of his or her left-to-right shunt physiology regardless of whether the great arteries are transposed and in spite of very complicated atrial or ventricular anatomy. Of course, it is possible for several of these types of physiology to coexist in the same patient. For example, the patient with truncus arteriosus may have the physiology of a left-to-right shunt from unrestricted blood flow to the pulmonary arteries and also have physiology similar to a patient with aortic regurgitation from an associated problem: severe truncal valve regurgitation. It is also likely that a specific category of structural cardiac defect will include patients with different types of physiology. For example, some infants with truncus arteriosus will have increased pulmonary blood flow and severe pulmonary edema similar to other patients with a large left-to-right shunt. However, those infants with truncus arteriosus and severe stenosis of the pulmonary ostia will have the physiology of a right-to-left shunt.

DEFINITION OF A LEFT-TO-RIGHT SHUNT

The patient with a left-to-right shunt has a higher blood flow to the pulmonary circulation than to the systemic circulation. The difference between the amount of blood delivered to the pulmonary circulation and that delivered to the systemic circulation equals the amount of already-oxygenated blood that is pumped back to the lungs, which equals the left-to-right shunt. The volume of deoxygenated blood delivered to the pulmonary circulation per minute is the usable or ''effective'' pulmonary blood flow. Calculation of the effective pulmonary blood flow and total pulmonary blood flow (Q_p) at cardiac catheterization is usually done with application of the Fick equation (Table 58–1) as discussed in Chapter 54. The left-to-right shunt is the total pulmonary blood flow minus the effective pulmonary blood flow. The pulmonary to systemic flow ratio (Q_p/Q_s) can be calculated without calculation of flows.

DETERMINANTS OF THE MAGNITUDE OF A LEFT-TO-RIGHT SHUNT

Clinical features of a left-to-right shunt are influenced by a number of variables. Included are the age of the patient, the anatomic location of the shunt, the size of the communication, and

Table 58–1. Calculation of Left-to-Right Shunt

1. Left-to-right shunt = $Q_p - Q_{ep}$
2. Q_p = pulmonary blood flow = $\frac{\text{Oxygen uptake}}{(\text{Pulm. artery } O_2 \text{ content} - \text{Left atrial } O_2 \text{ content})}$
3. Q_{ep} = effective pulmonary blood flow = $\frac{\text{Oxygen uptake}}{(\text{Pulm. venous } O_2 \text{ content} - \text{Mixed venous } O_2 \text{ content})}$
4. Pulmonary to systemic flow ratio = Q_p/Q_s = $\frac{\text{Aorta saturation} - \text{Mixed venous saturation}}{\text{Pulm. vein saturation} - \text{Pulm. artery saturation}}$

the relative resistances of the right- and left-sided circulations (Table 58–2). This chapter will furnish a brief overview of how these physiologic variables relate to the clinical features of the patient with a left-to-right shunt.

Age and Maturity of the Patient

The age and maturity of the patient influence the clinical features of a left-to-right shunt. The premature infant, because of relatively undeveloped pulmonary arteriolar musculature, develops a larger left-to-right shunt than does a more mature patient. A relatively small patent ductus arteriosus or ventricular septal defect in the premature infant may result in severe pulmonary edema. In contrast, a large ventricular septal defect or atrioventricular canal in a full-term newborn infant may be asymptomatic because of the high pulmonary vascular resistance that is present at the time of birth. The full-term infant with a large ventricular septal defect or atrioventricular canal is likely to develop symptoms of pulmonary edema by 4 to 6 weeks of age as pulmonary vascular resistance diminishes. Clinical manifestations of excessive pulmonary blood flow can develop such that surgical therapy in infancy is required.

In the era before surgery was available for these babies, those who survived infancy were observed to improve eventually in most cases. Typically there was a "golden period" between the severe heart failure of early infancy and symptomatic pulmonary vascular obstructive disease in the second decade of life. During this "golden period," the child developing pulmonary vascular disease was hemodynamically well balanced with minimal symptoms. Sequelae of pulmonary vascular obstructive disease developed in the older patient who had a left-to-right shunt earlier in life including cyanosis, hemoptysis, symptomatic right-sided heart failure, arrhythmias, and sudden death. A left-to-right shunt that is well tolerated in youth can become symptomatic with aging even without developing vascular disease. The shunt that was tolerated earlier in life may cause exercise intolerance, congestive heart failure, arrhythmias, or exacerbation of ventricular dysfunction in the older individual. Right-to-left shunting without pulmonary vascular disease may develop as a consequence of aging.

Table 58–2. Factors that Influence Clinical Features of a Left-to-Right Shunt

Age of the patient
Anatomic location of the shunt
Size of the communication between systemic and pulmonary circulation
Pulmonary and systemic resistance ratios (for post-tricuspid shunts)
Instantaneous interatrial pressure differences affected by compliance differences between the atria, differences in pulmonary and systemic venous compliance, and ventricular filling (for pretricuspid shunts)

Table 58–3. Pretricuspid Left-to-Right Shunts

Atrial septal defect
Secundum type
Primum type
Sinus venosus type
Coronary sinus type
Inferior vena caval type
Totally anomalous pulmonary venous connections, unobstructed
Partially anomalous pulmonary venous connection

Anatomic Location of the Shunt

The anatomic location of a left-to-right shunt will influence the clinical presentation. Lesions can be conveniently categorized as those resulting in a pretricuspid or a post-tricuspid left-to-right shunt (Tables 58–3 and 58–4). The prototype pretricuspid left-to-right shunt is the atrial septal defect. Typically, the patient with a pretricuspid shunt is mildly symptomatic or asymptomatic in infancy. There is usually increased pulmonary blood flow without pulmonary hypertension. Right ventricular volume overload results in right ventricular hypertrophy. The increased flow across the tricuspid valve causes a low-frequency diastolic rumble in the tricuspid area. Even with a high pulmonary-to-systemic flow ratio, in a pretricuspid shunt the risk of development of pulmonary vascular obstructive disease is low. Determinants of the magnitude of a pretricuspid left-to-right shunt include whether there is obstruction between the left- and right-sided circulations (e.g., the size of an atrial septal defect), the systemic and pulmonary venous capacitance, and the diastolic compliance of the right ventricle. The physiology of the left-to-right shunt in the atrial septal defect patient is discussed further in Chapter 60.

The prototype post-tricuspid left-to-right shunt is the ventricular septal defect. A patient with a large post-tricuspid shunt typically develops symptomatic pulmonary edema in infancy. Increased pulmonary blood flow is associated with pulmonary artery systolic hypertension unless the communication between the left- and right-sided circulation is stenotic. Volume overload of the left ventricle leads to left ventricular hypertrophy. Increased pulmonary venous return to the left atrium leads to excessive flow across the mitral valve and causes a low-frequency, diastolic murmur in the mitral area. If the left-to-right communication is not stenotic, pulmonary artery systolic hypertension is expected and eventual development of pulmonary vascular obstructive disease may occur. Determinants of the magnitude of a post-tricuspid left-to-right shunt include the size of the left-to-right communication (e.g., whether the ventricular septal defect is stenotic), the systemic vascular

Table 58–4. Post-Tricuspid Left-to-Right Shunts

Ventricular septal defect
Ruptured sinus of Valsalva (into RV)
Truncus arteriosus
Aorticopulmonary window
Aorticopulmonary fistula
Patent ductus arteriosus
Atrioventricular canal defect with ventricular component

Table 58–5. Characteristics of "Obligatory" Left-to-Right Shunts

Gerbode defect—left ventricular-to-right atrial defect
Atrioventricular canal with left ventricular-to-right atrial component (e.g., mitral regurgitation with ostium primum atrial septal defect)

resistance, and the pulmonary vascular resistance. The pulmonary vascular resistance is dependent upon the pulmonary arteriolar resistance and the pulmonary venous pressure. The physiology of the patient with a ventricular septal defect is discussed further in Chapter 59.

The patients with a left ventricular-to-right atrial shunt are considered to have an "obligatory" shunt (Table 58–5). The anatomic size of the communication between the right- and left-sided circulations (and to a minimal extent, right atrial compliance) determines the magnitude of an "obligatory" shunt. This is called "obligatory" since the left ventricular systolic and diastolic pressures are higher than the right atrial pressures throughout the cardiac cycle, causing shunting that is unaltered by the pulmonary vascular resistance and diastolic filling of the right ventricle. For this reason, pulmonary artery banding will not successfully palliate a patient with an obligatory shunt. The left ventricular-to-right atrial shunt has clinical physiologic features similar to a ventricular septal defect with a superimposed increase in tricuspid flow and right ventricular volume overload. Risk of development of pulmonary vascular disease is similar to a pretricuspid shunt (Table 58–6).

Table 58–6. Generalizations about Features of Pre- and Post-Tricuspid Left-to-Right Shunts

	Pretricuspid Shunt	*Post-tricuspid Shunt*
Murmur	systolic; pulmonary flow	systolic; at shunt
	diastolic; tricuspid rumble	disastolic; mitral flow rumble
Symptoms	uncommon in infancy	common in infancy
Pulmonary hypertension	unlikely	likely, if not restrictive
Electrocardiogram	right ventricular hypertrophy	left ventricular hypertrophy
Volume overload	of right ventricle	of left ventricle

Relative Resistances of the Right- and Left-Sided Circulations

The amount of left-to-right shunt in a patient with a large patent ductus arteriosus or aorticopulmonary window will decrease if pulmonary vascular resistance increases. The relative resistances of the pulmonary and systemic vascular beds determine the amount of left-to-right shunt in the case of a nonrestrictive communication at the level of the great arteries. For a shunt at the level of the ventricles which is nonrestrictive and in which there is not outflow obstruction of either ventricle, the magnitude of the shunt is also determined by the pulmonary and systemic resistances.

The magnitude of the shunt with a large atrial septal defect is determined by the instantaneous pressure differences between the right and left atrium during the cardiac cycle. Factors that affect these atrial pressures include the compliance of the atria, the resistance to ventricular filling (due to the diastolic compliance of the ventricle or due to an anatomic obstruction to ventricular filling), and the capacitance of the venous circuit to which the atrium is connected. It has been shown that one can find a right-to-left shunt across the atrial septal defect during some phases of the cardiac cycle (during and immediately after atrial systole) even though the net shunt is left-to-right as discussed in Chapter 60.

DEVELOPMENT OF PULMONARY VASCULAR OBSTRUCTIVE DISEASE

Pulmonary vascular obstructive disease is a devastating complication of left-to-right shunts. This important topic is discussed in great detail in Chapters 21 and 116 of this text. The tendency to develop pulmonary vascular obstructive disease involves a number of variables. The patient who has a post-tricuspid shunt that is anatomically large (and thus under high pressure) is at greatest risk for developing vascular disease. Pulmonary vascular obstructive disease does not usually occur at less than 1 year of age; however, vascular disease potentially develops as early as 6 months of age in patients with Down's syndrome and in patients in whom a cyanotic defect is associated with high pulmonary blood flow (e.g., tricuspid atresia with transposition, truncus arteriosus, or transposition of the great arteries with ventricular septal defect). Cardiac centers at high altitude have a much different clinical experience with their infants with anatomically large post-tricuspid communications than that which is observed in cardiac centers at sea level. Life at high altitude is associated with hypoxic pulmonary vasoconstriction (as discussed in Chapter 26), which decreases the severity of pulmonary edema in early infancy but increases the risk of children with left-to-right shunts being referred late and developing pulmonary vascular disease.

CHAPTER 59

Ventricular Septal Defect

Carl H Gumbiner
Atsuyoshi Takao

Ventricular septal defect (VSD) is the most common cardiac abnormality found in children. A practicing pediatric cardiologist encounters a patient with VSD nearly every day. Progress in the evaluation and management of ventricular septal defect over the past 40 years has paralleled and exemplified the evolution of pediatric cardiology as a medical discipline. Because of its frequency and because of the range of anatomic and physiologic disturbances that may constitute this abnormality, VSD remains a focus for the on-going evolution of anatomic terminology, invasive and noninvasive assessment technology, and therapeutic advancement. Management of the patient with ventricular septal defect represents both fundamental and state-of-the-art pediatric cardiology.

HISTORY

Although ventricular septal defect was a known anatomic entity much earlier, credit for its first clinical description is generally given to Roger's article published in 1879.[1] The phrase ''maladie de Roger'' is still used to refer to small VSD in the asymptomatic patient. When Eisenmenger described a patient with ventricular septal defect, cyanosis, and pulmonary hypertension,[2] this complex was regarded as a different and separate clinical entity. In her classic text, Abbott correlated the clinical findings of ventricular septal defect with the anatomic abnormality itself.[3] In an early attempt to explain the clinical differences among patients with VSD, Taussig attributed the presence or absence of symptoms to the location of the defect in the septum.[4] Later, studies began to relate the physiologic disturbance with the size of the defect in the septum.[5,6]

The earliest surgical treatment of ventricular septal defect was pulmonary artery banding.[7] Lillehei reported successful closure of VSD using the cross-circulation technique in 1955.[8] Soon thereafter, the advent of cardiopulmonary bypass made the intracardiac repair of ventricular septal defect a routine procedure. As surgical repair of VSD was becoming a reality, the effect of pulmonary vascular resistance on clinical course and surgical outcome was recognized.[9,10] In 1958, Heath and Edwards described the morphologic changes associated with pulmonary vascular disease,[11] and their six categories of vascular change have remained the standard of comparison to the present time. Lev's early descriptions of the anatomy of the conduction system in association with septal defects significantly enhanced surgical outcome by reducing the incidence of complete atrioventricular block.[12,13]

The technique of axial cineangiography provided the surgeon with far more specific preoperative delineation of the size, location, and number of defects.[14] Since 1979, real-time two-dimensional (2-D) echocardiography has dramatically improved the noninvasive anatomic assessment of ventricular septal defect and has resulted in an entirely new anatomic classification.[15–17]

DEFINITION

Although ventricular septal defect is one of the most common isolated congenital cardiac malformations, it is also frequently found in association with other lesions and found as part of more complex cardiac malformations. In this chapter, we consider VSD as an isolated condition, in the absence of a conotruncal malformation, and in the presence of two normally related ventricles. This discussion, therefore, does not include VSD as part of cono-

truncal malformations (i.e., persistent truncus arteriosus, transposition of the great arteries, tetralogy of Fallot, or double-outlet right ventricle). It also excludes all forms of univentricular heart and complete atrioventricular canal defect. We have also chosen to exclude discussion of VSD as part of a complex with associated lesions that are discussed elsewhere in this text, such as coarctation of the aorta and interrupted aortic arch.

Certain acquired conditions result from the presence of the ventricular septal defect itself, and therefore warrant consideration here. These include acquired right ventricular outflow tract obstruction, acquired left ventricular outflow tract obstruction, aortic regurgitation, and so-called aneurysm of the ventricular septum.

INCIDENCE AND PREVALENCE

Isolated ventricular septal defect accounts for approximately 20% of patients followed in large pediatric cardiology clinics.[18,19] In Mitchell's prospective study of 56,109 total births, the incidence of congenital heart disease was 8.14/1,000 births, and 29% of those children affected had ventricular septal defect.[20] Hoffman found a similar incidence of congenital heart disease and proportion of those with VSD.[21,22] Dickinson et al.[23] found the incidence of VSD in Liverpool to be 1.8/1,000 live births. Although most estimates have ranged from approximately 1.5 to 2.0/1000 live births,[18,22] evidence suggests that the incidence of ventricular septal defect in the United States has increased significantly in the past 15 years,[24] and may be as high as 2.6/1,000 live births.[25] This increased incidence is unexplained, but is not believed to be a function only of increased detection.[24]

ANATOMY

The nomenclature of ventricular septal defect has changed over the past decade due to the enhanced clinical ability to localize defects using the techniques of axial cineangiography and, more recently, real-time two-dimensional echocardiography. Precise localization of the defect, and the description thereof, is more than a semantic exercise. The location of the defect has implications for the likelihood of change in the size of the defect with time. Certain types of defects may predispose to secondary conditions, such as aortic regurgitation or subaortic obstruction. In a patient for whom surgery is contemplated, precise preoperative description of the defect may determine the surgeon's approach to the repair, usually tells him the relationship of the defect to the specialized conduction system, and helps determine the expected complications. Terminology must therefore facilitate communication between angiographers, echocardiographers, and surgeons, as well as embryologists and pathologists.

Roger's early description of ventricular septal defect was a clinical one with little anatomic reference.[1] Abbott described defects occurring in the subaortic region of the septum, or more rarely in the lower, muscular portion of the septum.[3] She noted a difference in location of the defect to be a determinant in the clinical course of the patient. Taussig's early text[4] described two types of defects: "simple" defects (maladie de Roger) and "high" defects with aortic override. Subsequent reports related clinical course to the size of the defect,[5,12,26] and the anatomic localization of defects included the concepts of "membranous" VSD and "outflow" VSD. Becu et al.[26] pointed out that the term "membranous" VSD was incorrect, but the phrase was widely used until the mid 1970's.

A clinically useful classification scheme divides ventricular septal defects into four types: I, II, III, and IV.[27] Type I, or so-called "supracristal" defects, lie just beneath the pulmonic valve and communicate with the right ventricular outflow tract above the supraventricular crest. They comprise approximately 5% of defects seen in this country,[19] and are associated with a significant incidence of aortic regurgitation. Type II defects, the "infracristal" or "membranous" defects, are the most common types found, accounting for up to 80% of defects.[19] Type III defects, located in the posterior region of the septum, beneath the septal leaflet of the tricuspid valve, are often associated with left axis deviation on the surface electrocardiogram, and are also referred to as "atrioventricular canal type" defects. Approximately 8 to 10% of ventricular septal defects are of this type.[19] Type IV defects, found in 5 to 20% of patients with VSD,[19] are bounded entirely by muscular septum and are often multiple. This scheme, while appealingly simple, has never been ideal for embryologists and anatomists, and is inadequate to describe the location and boundaries of the defects as they are delineated by current cineangiography and real-time 2-D echocardiography. It has been replaced with a somewhat complex, but more descriptive, classification[15–17,28–33] described below.

The intact interventricular septum is a complex, non-planar, helical structure which can be divided into four zones according to landmarks on its right ventricular aspect (Fig. 59–1A). The inlet septum is predominantly smooth walled and extends from the septal attachment of the tricuspid valve leaflets to the distal attachment of the tricuspid tensor apparatus. The apical trabecular zone separates the coarse trabecular portion of the right ventricle from the finely trabeculated left ventricular apical septum. The smooth-walled outlet, or infundibular, septum is separated from the trabecular portion of the septum by the septal band[26] or the trabeculae marginalis.[28,31] These three muscular zones radiate from the small membranous septum, which lies adjacent to the anteroseptal tricuspid commissure on the right side, and adjacent to the right posterior aortic commissure and anterior mitral valve leaflet on the left side (Fig. 59–1B). The term "crista supraventricularis" designates a muscular zone in the normal heart separating the tricuspid and pulmonary valves, as well as the pulmonary and aortic valves.[28] Defects in the ventricular septum may be adjacent to the membranous septum or may lie entirely within the muscular septum. Complete absence of the membranous septum seldom occurs with simple VSD. Furthermore, defects adjacent to the membranous septum have a partial margin consisting of muscle. For these reasons, the term "membranous" defect has been replaced by the more anatomically correct "perimembranous" defect. Perimembranous defects are divided into three major subtypes (Fig. 59–2A), according to the adjacent portion of muscular septum: perimembranous inlet, perimembranous trabecular, and perimembranous outlet defects.[15,28–31,33,34] Perimembranous inlet defects (included in other classifications as AV canal type defects and Type III defects) lie posterior to the septal leaflet of the tricuspid valve. Perimembranous trabecular defects comprise the most common group of simple VSDs, and are the majority of previously designated Type II defects. Perimembranous outlet defects comprise a portion of previously designated Type I defects (along with muscular defects of the outlet septum). Depending on

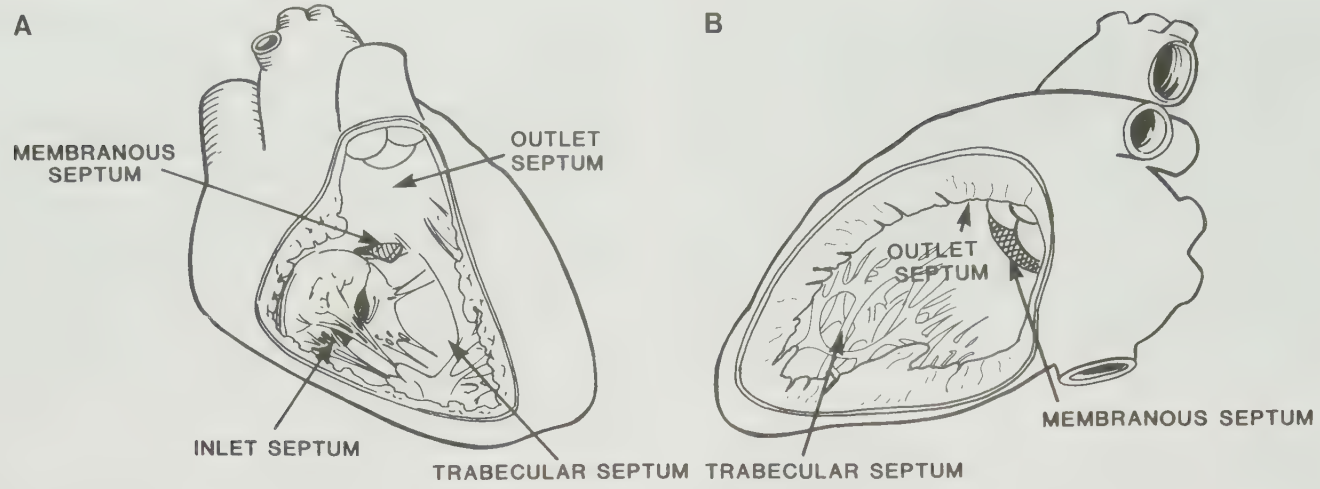

Fig. 59–1. Schematic representation of the regions of the ventricular septum from *A*. the right ventricular aspect, and *B*. the left ventricular aspect.

size and shape of a perimembranous defect, it may overlap two or more of the three categories. By virtue of adjacency to the membranous septum, all perimembranous defects are subaortic[33] (Fig. 59–2B).

Muscular ventricular septal defects, bounded entirely by a muscular rim, may also be divided into three categories: inlet, trabecular, and infundibular. Muscular trabecular defects (previously designated Type IV defects) may be multiple and have given rise to the graphic phrase "Swiss cheese septum."[35]

Defects of the outlet septum beneath the pulmonic valve have caused particular controversy in classification. The term "supracristal" defect is inaccurate because: a) position relative to the crista is, in fact, variable; b) the crista, a landmark of the normal septum, is often distorted or absent in the presence of ventricular septal defect; and c) the importance of defects in this position is not based on their position relative to the muscular crista, but to the semilunar valves. Often, these defects are termed "subpulmonic."[36] Perimembranous outlet defects are subaortic as well, however, so the presently preferred label is the somewhat cumbersome "doubly committed subarterial defect."[28,30,31,33] These defects, more common in Oriental populations,[37] often undermine the muscular support of the right coronary cusp of the aortic valve and may be associated with aortic regurgitation.

Defects of the inlet septum—particularly perimembranous inlet defects—may involve some degree of malalignment of the ventricular septum with the atrial septum. In such defects, there is generally overriding or straddling of the tricuspid or mitral valve.[15] Perimembranous defects of the outlet septum may be associated with malalignment of the ventricular septum with the infundibular septum.[15] This may occur occasionally in isolated VSD,[38,39] but is, of course, more usually associated with more complex conotruncal malformations, such as persistent truncus arteriosus or tetralogy of Fallot.

The relationship of the specialized atrioventricular conduction system to defects of the ventricular septum has been a subject of investigation since the early work by Lev[13] and Truex[40] in the late 1950s. This information is critical to the surgeon faced with repair of these defects. With perimembranous defects, and normally re-

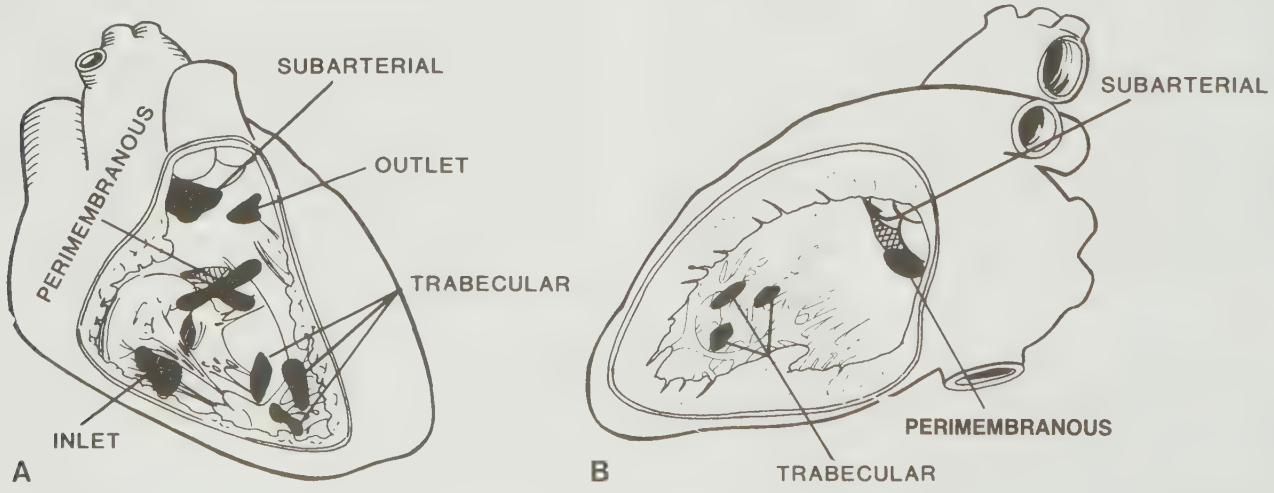

Fig. 59–2. Schematic representation of the location of various types of ventricular septal defect from *A*. the right ventricular aspect, and *B*. the left ventricular aspect.

lated ventricles, the atrioventricular conduction tissue is always related to the posterior inferior aspect of the defect itself.[13,28,31,40,41] In muscular defects, the atrioventricular conduction tissue maintains its position at the margin of the membranous septum and will hence lie superior and anterior to the defect[28,31] and usually separate from it. With ventricular inversion, the conduction tissue lies anterior to the VSD. This is discussed fully in Chapter 73.

Associated Conditions

Ventricular septal defect is present in many complex structural heart anomalies, which are considered elsewhere in this book. Certain associated conditions, however, arise because of the ventricular defect itself. These include secondary aortic regurgitation, subaortic obstruction, and right ventricular outflow tract obstruction.

Aortic regurgitation with ''doubly committed subarterial'' (type I) ventricular septal defect is a well-known association.[36,42–49] It is due to the poorly supported right coronary cusp, combined with a Venturi effect produced by the VSD jet.[50] Prevalence of this association is approximately 3% of ventricular septal defects in this country.[43] The incidence of subarterial ventricular septal defect (and associated aortic regurgitation) is substantially higher (up to 20 to 30% of patients with VSD) among Oriental populations.[36,37]

A less well-defined, and possibly less common, associated condition is ventricular septal defect with discreet fibrous subaortic stenosis. This has been described by several investigators[51–55] and may represent an incidental association[52] or, in many cases, may be a direct result of septal malalignment and secondary development of a fibrous ridge.[55] Its significance lies in the potential development of left ventricular outflow tract obstruction in patients with small or surgically corrected ventricular septal defect.

Right ventricular outflow tract obstruction occurs secondary to ventricular septal defect in 3%[56] to 7%[57] of patients. This is generally due to hypertrophy of anomalous muscle bundles,[58] although it may result from septal malalignment.[59]

Perimembranous ventricular septal defects are often associated with ''aneurysm'' of the ventricular septum.[60] This phenomena is thought, in part, to be responsible for the decrease in size and/or spontaneous closure seen in up to 40% of patients with these defects.[61] Morphologic,[62,63] angiographic,[64] and echocardiographic[65] studies have demonstrated such aneurysms rarely to be composed of septal tissue and most often composed of adherent or reduplicated tricuspid valve tissue.[63,65] This occurs most frequently with perimembranous trabecular defects, but this adherence of tricuspid valve tissue does not occur with defects of the outlet septum, which seldom close spontaneously. True aneurysm of the ventricular septum does occur occasionally and may produce right ventricular outflow tract obstruction.[66]

EMBRYOLOGY

The embryologic formation of the normal ventricular septum has been described in a number of elegant studies.[67–70] After cardiac looping at 23 to 25 days gestation, the primitive left ventricle, formed from the ventricular portion and the primitive right ventricle, formed from the proximal portion of the bulbis cordis, are connected by the primary interventricular foramen. Growth and trabeculation of the ventricles accounts for formation of the major portion of the muscular septum as the medial walls of the ventricles become apposed and fuse together.[68,69] While the ventricles enlarge, the atrioventricular canal moves rightward, such that the atria communicate with the primitive right ventricle. As this happens, the plane of the primary interventricular foramen shifts leftward, and, as the interventricular foramen II, it gives access from the left ventricle to the posteromedial portion of the conus cordis. The conus swellings appear at approximately the same time as the truncal swellings and the atrioventricular cushions. They ultimately merge to form the conus septum, separating the conus cordis into the anterolateral and posteromedial portions.

The conus septum also separates the interventricular foramen (now foramen III) from the AV canal. Completion of the interventricular septum is accomplished by fusion of endocardial cushion tissue from the conus septum, with the superior portion of the muscular septum and a portion of the right superior endocardial cushion.[67,68] With this fusion, the interventricular foramen III is closed. Later, this portion of the septum thins to become the membranous interventricular septum.

The formation of the membranous and perimembranous septum is a late and multifaceted developmental event and is subject to numerous aberrations that may manifest later as perimembranous ventricular septal defect.[70] Defects of the outlet septum are felt to represent failure of fusion of portions of the conus septum.[67] Inlet defects may represent failure or complete fusion of the right superior endocardial cushion tissue with the muscular septum. Muscular defects, particularly in the trabecular septum, are probably due to excessive excavation of the septum during the growth of the ventricle, or inadequate merger of the medial walls of the ventricles.

PHYSIOLOGY

The presence of a defect in the ventricular septum, and the consequent communication between the systemic circulation and the pulmonary circulation at that level, may have two adverse effects: altered hemodynamics because of a left-to-right shunt, and an altered pulmonary vascular bed. While mutually related, these are separate effects that are best considered individually.

The phrase ''left-to-right'' shunt implies the recirculation of oxygenated (pulmonary venous) blood through the pulmonary capillary bed. When it occurs at the ventricular level, the magnitude of left-to-right shunting is dependent upon the size of the ventricular septal defect and upon the resistance in the pulmonary vascular bed. Defects are generally divided into three categories: small, moderate and large, based not only on physical size, but also on circulatory dynamics, although there is a general correlation between the two. Various distinguishing criteria have been proposed.[18,19,71–73] Small defects limit flow and restrict pressure equalization between the ventricles. The left-to-right shunt is small, and right ventricular pressure is normal or minimally elevated. Large defects offer little resistance to flow and have equal pressure in the ventricles. The magnitude of the left-to-right shunt is entirely dependent on relative pulmonary and systemic vascular resistance. Anatomically, large defects are those equal to or greater in size than the cross-sectional area of the aortic root.[71] Moderate-size defects are those that offer resistance to pressure, but usually little resistance to flow. The right ventricular pressure is less than that of the left ventricle, but is often elevated above normal. In moderate defects, the magnitude of the left-to-right shunt is dependent

on both the size of the defect and the pulmonary vascular resistance.

There has been considerable discussion on the influence of the location of the VSD on its physiologic effect.[10] Presently there is little evidence to suggest that location of the defect (e.g., muscular trabecular vs. perimembranous outlet) is a significant determinant of either shunt or resistance, per se. A question has also been raised about the effect of change in size or shape of the defect with septal contraction during the cardiac cycle. This phenomenon occurs with small defects, but is probably insignificant with moderate or large ones. It may well influence the murmur characteristics of small defects, but is probably irrelevant to hemodynamic considerations.

A left-to-right shunt at the ventricular level has three adverse hemodynamic consequences: 1) left ventricular volume overload, 2) pulmonary overcirculation, 3) compromise of systemic cardiac output. The increased volume demand on the left ventricle results in dilation and hypertrophy. The former produces elevation of end-diastolic pressure by virtue of the familiar length-tension relationship.[74] The latter minimizes wall tension increase, but, by altering myocardial compliance, further aggravates the increase in end-diastolic left ventricular pressure. This elevation in end-diastolic pressure is reflected in increased left atrial pressure and consequently in pulmonary venous pressure.

Pulmonary overcirculation tends to increase the pressure in the pulmonary capillary bed, altering its pressure relationship with the pulmonary interstitial space. An abnormal equilibrium is established, with a resultant increase in pulmonary interstitial fluid.[75] This alters pulmonary compliance[76] and, to a lesser extent, pulmonary gas exchange. In its severe form, increased pulmonary interstitial fluid may manifest as frank pulmonary edema, but lesser degrees of interstitial edema also have an adverse influence upon pulmonary function.

The increased pressure of the pulmonary capillary bed is a function of both pulmonary overcirculation and elevated pulmonary venous pressure, due to left ventricular volume overload. This is evident from observation of patients with other conditions. The pulmonary overcirculation associated with atrial septal defect tends to have less effect on pulmonary compliance largely because the left atrium is "vented" and the left ventricular end-diastolic pressure is not elevated.[75] Conversely, myocardial abnormalities producing only modest elevation of left-sided filling pressures are often well tolerated in the absence of pulmonary overcirculation.

Pulmonary recirculation by the left ventricle is accomplished at the expense of systemic blood flow or cardiac output. Compensatory mechanisms maintain organ perfusion and blood pressure. These include increased circulating catecholamines and increased activity of the sympathetic nervous system, both serving to increase systemic vascular resistance. Decreased renal blood flow tends to evoke the retention of sodium and water retention via the renin-angiotensin system.[77] This, in turn, raises both systemic and pulmonary venous pressure, promoting formation of both systemic and pulmonary interstitial edema.

The magnitude of these effects is a function of the size of the left-to-right shunt, which is, as mentioned above, dependent upon pulmonary vascular resistance, as well as anatomic size of the ventricular septal defect. The terms "pulmonary hypertension," "high pulmonary resistance," and "pulmonary vascular disease," often used interchangeably, must not be confused with each other. As pressure is determined by flow and resistance, elevated pulmonary artery pressure (i.e., pulmonary hypertension) may result from a predominant increase in flow or from a predominant increase in resistance. In the former, a VSD with pulmonary hypertension may manifest all the physiologic consequences of a large left-to-right shunt. With high resistance, however, a VSD with pulmonary hypertension may show little evidence of LV volume overload or pulmonary interstitial fluid formation.

Pulmonary resistance is a function of numerous factors, including age,[78] altitude,[9] hematocrit,[79] level of activity,[80] and structural integrity of the pulmonary vascular bed.[11,81,82] It should not be equated with pulmonary vascular obstructive disease—one cause of elevated pulmonary vascular resistance. Pulmonary vascular resistance is elevated in the normal newborn,[22,71] and clinical manifestations of left-to-right shunting are unusual in this age group. This elevation of resistance is primarily due to increased medial wall thickening of muscular arterioles,[83,84] although Lister et al.[78] pointed out the effect of increased hematocrit in those infants as well. Premature infants are prone to a more early manifestation of left-to-right shunting, presumably because of decreased development of small, muscular arterioles.[84]

Pulmonary vascular resistance usually declines in the first three months of life, with increase in flow, although this process is inhibited in the presence of an existing left-to-right shunt, lung disease, or residence at higher elevations. Vogel et al.[9] compared the incidence of symptomatic congestive heart failure among infants with ventricular septal defect living in Colorado with those living in Texas. They found significantly fewer patients demonstrating congestive heart failure and attributed this phenomenon to the lower oxygen tension in Colorado and its effect on pulmonary vascular resistance.

Pulmonary vascular disease, as described by Heath and Edwards[11] and others[8,82,85] may develop as a consequence of left-to-right shunting. This usually follows a period of decreased resistance and high flow, but may occur in patients who never manifest a large left-to-right shunt.[86,87] The ultimate consequences of pulmonary vascular obstructive disease are irreversible vascular changes and pulmonary resistance equal to or exceeding systemic resistance. The latter causes reversed shunting (right-to-left) at the ventricular level and systemic arterial oxygen desaturation, or cyanosis. This combination of ventricular septal defect, pulmonary vascular disease, and cyanosis is termed Eisenmenger's complex.[10] In combination with other systemic-pulmonary communications, pulmonary vascular disease and cyanosis are referred to as the Eisenmenger syndrome.[10]

Experimental Models

Several investigators have successfully created animal models of ventricular septal defect for evaluation of left-to-right shunt physiology, medical intervention, and diagnostic techniques. Strains of animals with congenital VSD have not been reported; but surgically created defects have been reported since 1925.[88] Griffin and Essex were able to create defects of known size in dogs and study their chronic effect on blood volume, hemoglobin, and the dogs' electrocardiograms.[88]

In 1970, Mesel reported a study of acutely instrumented dogs in which electromagnetic flow probes were wedged into surgically created ventricular septal defects.[89] He correlated flow across the defect with pulmonary blood flow measured by the Fick technique.

He also demonstrated flow across the defect, amounting to 15 to 25% of total left-to-right shunt.[89]

Syndhorst et al., also using an acute canine model, created ventricular septal defects of known size by insertion of a flanged prosthesis into the muscular septum.[90] They demonstrated a salutary effect on left-to-right shunt hemodynamics with pharmacologic lowering of systemic vascular resistance. Boucek et al. reported similar findings with afterload-reducing agents administered to chronically instrumented lambs with surgically created ventricular septal defects.[91] Their work is particularly significant for their use of an immature animal model of what is, from a therapeutic standpoint, basically a pediatric condition. Sherman et al. used a VSD model in open-chested dogs to assess the utility of color-flow Doppler mapping in detection of ventricular septal defect.[92] The near future will doubtless see other investigators making use of animal models—most probably chronic models in immature animals—to assess newer diagnostic and therapeutic techniques.

CLINICAL MANIFESTATIONS

The clinical presentation and manifestations of children with ventricular septal defect have been reviewed in numerous articles and texts.[6,18,19,22,71,93,94] The wide spectrum of symptoms and physical findings relates to the size of the defect and the magnitude of the left-to-right shunt.

Small Defects

Small defects are associated with mild symptoms or, more commonly, with none at all. Patients most often come to the attention of the cardiologist because of a murmur detected on routine examination or at the time of an incidental illness. Pulmonary vascular resistance, elevated in the normal newborn, declines rapidly over the first few weeks of life,[71] creating a large pressure-gradient between left ventricle and right ventricle, usually with a loud murmur. The murmur is most often detected between 2 and 6 weeks of age. Not infrequently, however, it may be heard in the second or third day of life, prior to dismissal from the newborn nursery. In these cases, one can infer a very rapid decline in pulmonary vascular resistance, and almost invariably, a small defect. Other conditions producing a murmur that mimics that of VSD must be excluded, especially tricuspid regurgitation. A murmur heard in the first 18 hours of life is seldom due to isolated ventricular septal defect. Murmurs that appear later than the fourth month of life are seldom due to isolated small VSD. Late appearance of the murmur implies a delayed decline in pulmonary vascular resistance, and hence a larger defect or a different lesion. Of course, a murmur may be overlooked in the examination of a crying child, so attention must be paid to the frequency and circumstances of prior examinations. The murmur of small ventricular septal defect does not appear de novo in a child older than 6 months.

A small ventricular septal defect usually causes no symptoms. While a small left-to-right shunt may slightly alter pulmonary compliance with resultant mild tachypnea, this does not usually interfere with feeding or normal weight gain. In the older infant and child, the presence of symptoms is inconsistent with the diagnosis of small VSD.

The abnormal physical findings are primarily those of the cardiac examination. With the possible exception of mild tachypnea, the vital signs are usually normal. The lungs are clear. There is little evidence of systemic fluid retention and no jugular venous distension, hepatomegaly, or edema. Physical assessment of cardiac size in an infant is difficult. The precordial impulse may be mildly hyperactive, or most often is normal, although a systolic thrill along the left sternal border may be present. The second heart sound may be obscured entirely by the murmur, but when audible is of normal intensity. Physiologic splitting of second heart sound is usually present, but is often difficult to appreciate in the infant.

The murmur of ventricular septal defect is characteristically a harsh holosystolic murmur, heard loudest along the lower left sternal border. Small defects tend to produce a murmur of a somewhat higher pitch, but this is not a constant feature. On the other hand, a high-pitched or "squeaky" holosystolic murmur implies a small defect. The murmur may have a marked change in quality during systole or may not be holosystolic. This is most often due to change in size or shape of the defect with septal contraction and, once again, implies a small defect.

The location of the murmur is variable. Loud murmurs are usually heard over the entire precordium, and occasionally may be referred to the back. Localization of the murmur to the left third or fourth intercostal space also implies a small defect. Some observers have associated a murmur low along the left sternal border with a muscular defect, and a murmur heard high along the left sternal border with an outlet defect,[95] but these features are inconsistent and quite dependent upon the examiner. In older infants and children, small ventricular septal defect does not produce a diastolic murmur. In small infants, a soft diastolic filling sound may be present along the lower left sternal border. A louder flow rumble implies a larger defect with a significant left-to-right shunt.

Moderate-Size Defects

In the presence of a moderate size ventricular septal defect, the normal decline in pulmonary vascular resistance is somewhat delayed,[22,71] so detection of a murmur in the newborn period is uncommon. More often, a murmur is detected between 2 and 6 weeks of age, and may change in quality over several weeks as resistance continues to fall. The appearance of the murmur usually precedes the presence of significant symptoms in the child, but depending on the time of its detection, signs and symptoms may or may not be present.

Early signs of moderate size ventricular septal defect may be subtle and may suggest a small defect. These include mild tachypnea and mild tachycardia. As left-to-right shunting increases, signs and symptoms become more evident. Pulmonary compliance is abnormal, so that tachypnea is usually present and may be associated with increased work of breathing. This is especially true during feeding, with consequent compromise of caloric intake and resultant poor weight gain. With decreased pulmonary compliance there is frequently a history of one or more episodes of pneumonia, often as the presenting complaint leading to the detection of a murmur. Upper respiratory infections are also a frequent complaint, although this rather subjective observation is less easy to relate to the physiologic disturbance of a left-to-right shunt.

Sweating, especially with feeding, is a frequent manifestation of congestive heart failure in infants and is due to increased activity of the sympathetic nervous system. This finding is valuable in

very young infants, but is extremely nonspecific in infants greater than six months of age. If an infant "sweats the bedclothes through," this is more likely to be significant.

Physical findings with moderate size VSD reflect the size of the left-to-right shunt and degree of congestive heart failure. While moderate size defects tend to have smaller shunts than large defects (depending on resistance), the classification of the defect as moderate does not preclude significant congestive heart failure. The infant may be tachypneic but only rarely has intercostal or suprasternal retractions, or expiratory grunting. Resting heart rate is increased. The infants usually show poor weight gain. Often the decline in weight percentile has its onset at 2 to 4 months, reflecting the time of fall of pulmonary vascular resistance. Longitudinal growth is usually normal. Because of compromised systemic output and vasoconstriction, the infants may be pale and are often diaphoretic. Peripheral pulses are usually normal. There may be prominent neck veins in the upright position. The liver is usually palpable and may be significantly enlarged with a firm, rounded margin. Splenomegaly usually does not accompany significant hepatomegaly. Pulmonary rales may be present but are a late finding and indicate marked congestive heart failure or pneumonia.

The precordial impulse is increased in intensity and a precordial thrill is often present. The first heart sound is normal, and the second heart sound is usually obscured. If audible, the second heart sound may be single or narrowly split, with an accentuated pulmonary component. The harsh holosystolic murmur is usually low in pitch and can be heard over the entire precordium, the loudest at the lower left sternal border. A diastolic filling sound is often present. A low-pitched, mid-diastolic rumble, thought to be due to increased flow through the mitral valve, is present if the left-to-right shunt is large. Clinicians often relate the presence or absence of a flow rumble to the size of the shunt, and it is felt that a flow rumble is rarely evident with pulmonary-to-systemic flow ratios of less than 2:1.

Older children with moderate size defects do not develop signs and symptoms of congestive heart failure. Those with large left-to-right shunts manifest symptoms earlier and are treated or improve. Those with elevated pulmonary vascular resistance may present to the clinician later, but do not demonstrate evidence of congestive heart failure (see below).

Large Defects

The manifestations of large ventricular septal defect are similar to those of moderate size defects with high flow. Presentation is often delayed until the third or fourth month of life, when pulmonary vascular resistance falls. At that time, signs and symptoms of congestive heart failure may rapidly progress. They include the respiratory symptoms mentioned above, along with poor weight gain, diaphoresis, and frequent lower respiratory tract infections. These infants are often irritable. When failure is severe and long-standing, longitudinal growth may be impaired, as well as weight gain.

Likewise, physical findings are those of congestive heart failure with tachycardia, tachypnea, neck vein distension, and hepatomegaly. If failure is severe or if there is superimposed pneumonia, there may also be retractions and grunting. Peripheral edema is unusual in infants, even with severe congestive heart failure, and pulmonary rales are a late finding.

Precordial activity is increased, with a left parasternal lift. A systolic thrill is less common with a large defect than with a moderate defect—relating the thrill less to the flow across the defect than to the pressure gradient. The murmur is a low-pitched, holosystolic sound, poorly localized, and there is usually a diastolic flow rumble audible at the lower left sternal border.

Ventricular Septal Defect with High Pulmonary Vascular Resistance

The typical manifestations of ventricular septal defect—the harsh holosystolic murmur and evident congestive heart failure—are dependent upon substantial left-to-right shunt through the defect. In children with large defects (and occasionally moderate size defects) with high pulmonary vascular resistance, findings may be far more subtle, or may be different entirely. As mentioned, the normal elevation of pulmonary vascular resistance in the newborn delays the appearance of a murmur and the appearance of symptoms at that time. Careful palpation of the precordium in these infants will disclose a prominent right ventricular impulse, and auscultation reveals an enhanced second heart sound. Similar findings will be present in older infants in whom persistent elevation of pulmonary vascular resistance precludes the appearance of a typical holosystolic murmur. These infants may display respiratory symptoms and impaired weight gain, or may be asymptomatic. Referral to a cardiologist is often late because of the absence of significant murmur. Occasionally, parents will report the child to have cyanosis, especially with crying, indicative of right-to-left shunting through the defect.

Older children with large ventricular defect and pulmonary vascular obstructive disease have little complaint of respiratory symptoms, except with exertion. They may be only mildly cyanotic at rest, but develop profound reduction in O_2 saturation with exercise, which they tolerate poorly. There is often clubbing of the fingernails. A right ventricular parasternal lift is indicative of right ventricular hypertrophy, but the increased precordial activity felt with high flow ventricular septal defect is less evident. The second heart sound is markedly accentuated and well heard because the systolic murmur is a quiet one, if present at all. There is seldom a diastolic rumble, but a short early diastolic murmur of pulmonary regurgitation ("Graham Steele") may be heard.

ELECTROCARDIOGRAPHIC FEATURES

The electrocardiogram of the child with ventricular septal defect reflects the severity of the hemodynamic disturbance. With small VSD, the electrocardiogram is usually normal. Occasionally, a deeper-than-normal S wave in the right precordial leads or a mildly increased R wave in lead V_5 or V_6 will indicate mild left ventricular hypertrophy associated with the volume overload of the left ventricle. This feature, however, is usually masked by the normal prominence of right-sided forces in the newborn and young infant. In older children with small ventricular septal defect, the electrocardiogram is generally normal.

With moderate-size defects, the ECG usually shows some degree of left ventricular hypertrophy. Right ventricular hypertrophy may also be evident, depending on pulmonary artery pressure. Electrocardiographic evidence of left atrial enlargement may occasionally be noted but is uncommon, even in the presence of large pulmonary blood flow and large venous return to the left atrium.

Large defects may also manifest left ventricular hypertrophy on surface electrocardiogram, but nearly always there is evidence of combined right and left ventricular hypertrophy in the form of large, equiphasic voltage recordings in the midprecordial leads (Katz-Wachtel phenomenon).[96] Right axis deviation of the frontal plane QRS vector often accompanies the combined ventricular hypertrophy of large VSD. Older children with VSD and pulmonary vascular obstructive disease may have predominantly right ventricular hypertrophy on electrocardiogram. A pattern of pure right ventricular hypertrophy in infants and small children (beyond that normal for age), renders the diagnosis of isolated VSD suspect.

Perimembranous defects of the inlet septum may be associated with an electrocardiographic pattern of left axis deviation of the frontal plane QRS vector, with Q waves in standard leads I and AVL. This pattern, characteristic of atrio-ventricular canal defects, suggests an abnormal position of the specialized conduction system. One explanation for the left axis deviation is early separation of the left posterior fascicle from the left bundle branch.[97]

RADIOGRAPHIC FEATURES

As with the electrocardiogram, the radiographic findings of a patient with ventricular septal defect are not specific for that anatomic malformation, but reflect the size of the left-to-right shunt and the state of the pulmonary vascular bed. With small defects, the chest roentgenogram is usually normal. Occasionally there is a left ventricular contour to the cardiac silhouette, with a slight displacement of the cardiac apex downward and to the left. Pulmonary vascular markings may be mildly prominent as well, indicating the modest increase in pulmonary blood flow.

With moderate-size defects, the cardiac silhouette is enlarged, with a prominent left ventricular contour (Fig. 59–3). If pulmonary hypertension is present, the right ventricle may be enlarged as well, most evident as a "filling in" of the retrosternal space on a lateral projection. The left atrium is usually enlarged. On posterior-anterior projection, this may be evidenced by uplifting of the air column of the left mainstem bronchus. In lateral projection, the left atrium bulges posteriorly, often displacing the esophageal air column. This finding is evident on plain film, but is more dramatically illustrated with a barium swallow examination. The increased pulmonary blood flow is evidenced by enhancement of the pulmonary vascular markings, both centrally and peripherally. With pulmonary hypertension, the hilar markings may be more prominent than the peripheral markings, and the main pulmonary artery segment may be dilated. With large left-to-right shunts and congestive heart failure, interstitial edema, alveolar fluid, and Kerley B lines (indicating pulmonary venous engorgement) may be present. The reduced pulmonary compliance and increased respiratory effort are often reflected by chest hyperexpansion and flattening of the diaphragms.

Large defects with high flow show cardiomegaly with a more globular cardiac silhouette, due to right and left ventricular, as well as left atrial, and occasionally right atrial, enlargement (Fig. 59–4). The lateral projection shows a "filling in" of the retrosternal space and posterior enlargement of the left atrium. Pulmonary vessels are engorged, the lungs are usually hyperexpanded, and interstitial edema is often evident.

In older children with large defects and pulmonary vascular obstructive disease, the heart size is normal or mildly enlarged. Hypertrophy and dilation of the right ventricle may be evident by the anterior widening in the lateral projection. The main pulmonary artery segment is usually dilated and the central hilar vascular markings appear engorged, with peripheral markings normal or diminished (Fig. 59–5).

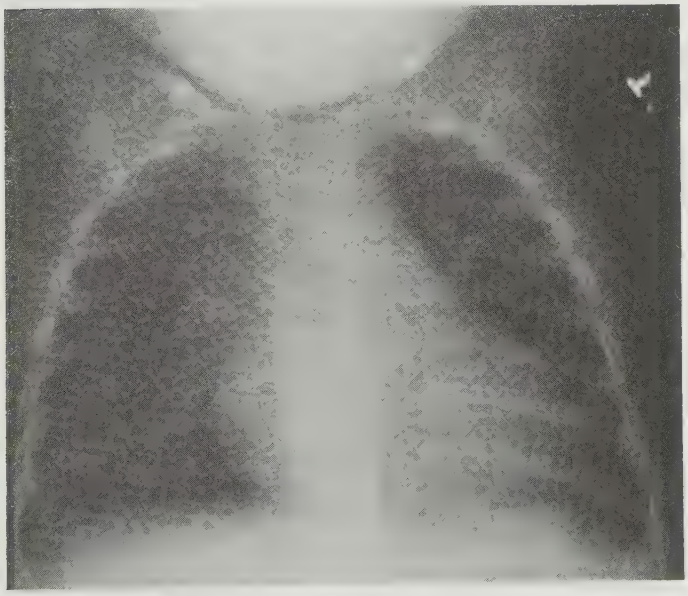

Fig. 59–3. Chest roentgenogram of a child with a moderately sized ventricular septal defect. The heart is enlarged. Pulmonary vascular markings are accentuated.

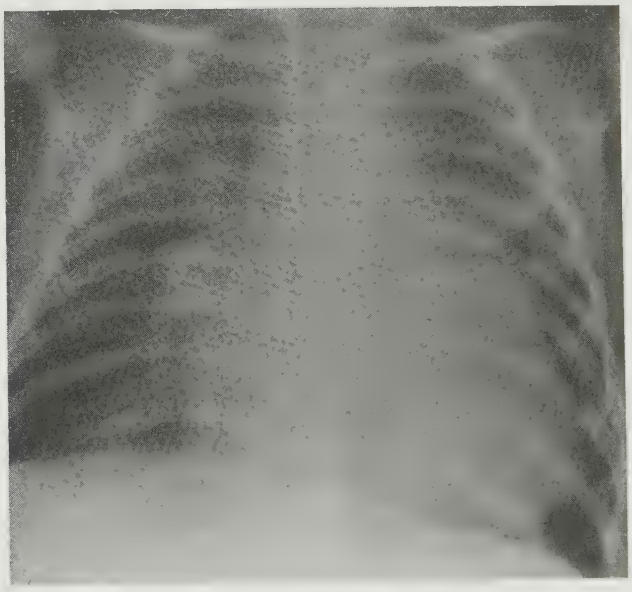

Fig. 59–4. Chest roentgenogram of an infant with a large ventricular septal defect. The cardiac silhouette is globular and significantly enlarged. Pulmonary vascular markings are accentuated, and evidence exists of pulmonary edema.

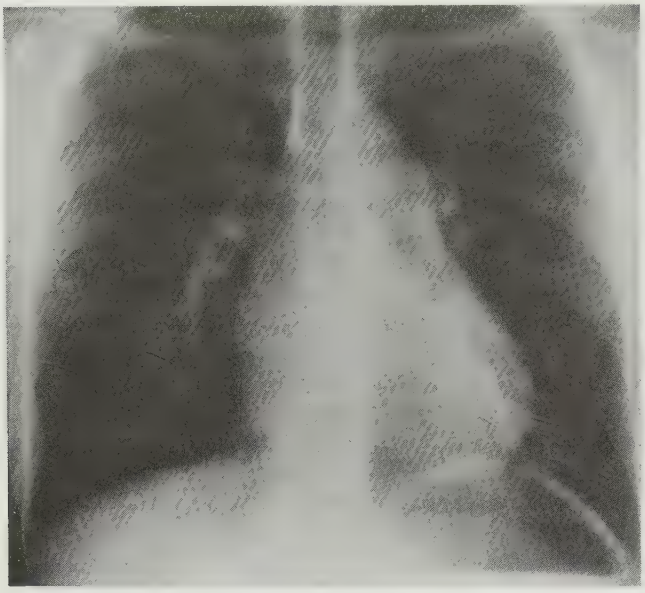

Fig. 59–5. Chest roentgenogram of an older child with ventricular septal defect and severe pulmonary vascular disease. The heart is only minimally enlarged. The main pulmonary artery segment is enlarged. The central hilar pulmonary markings are accentuated. The vascular markings in the peripheral lung fields are diminished.

ECHOCARDIOGRAPHY

The utility of echocardiography in the diagnosis and assessment of ventricular septal defect has progressed over the past 12 years in a fashion closely paralleling the advance of cardiac ultrasound technology: from M-mode to real-time 2-dimensional imaging techniques, and from pulsed Doppler through continuous wave and color-flow Doppler study.

Early M-mode echocardiography was useful for indirect assessment of the hemodynamic abnormality associated with left-to-right shunting.[98] In the presence of large left-to-right shunts, left atrial and left ventricular dilation can be demonstrated, although neither left atrial size[99] nor left atrial-to-aortic root diameter ratio[100] are reliably correlated to measured pulmonary blood flow. Demonstration of septal discontinuity on M-mode scan is unreliable for detection of all but the largest defects.[98,99] Systolic fluttering of the tricuspid valve has been cited as an M-mode feature of certain defects,[101] but this finding has limited diagnostic value.

Currently, M-mode echocardiography remains a useful adjunct to the assessment of patients with VSD, not in the visualization of the defect itself, but in the indirect assessment of pulmonary artery pressure. The M-mode pattern of pulmonary valve motion[98] and the right ventricular systolic time intervals, as measured from the M-mode echocardiogram,[102] may be helpful in estimation and longitudinal followup of pulmonary artery pressure.

Real-time 2-dimensional (2-D) echocardiography became a clinically useful modality in the mid-1970s[98,103] and was rapidly adapted to the evaluation of children with congenital heart disease.[104] Two studies early in the 1980s[105,106] described reasonable sensitivity and specificity of 2-D echocardiography for the detection of ventricular septal defects. Subsequent reports[15–17,98,107] attest to the increased accuracy of this technique acquired with experience and improved technology. Canale et al.[107] pointed out the value of the "T artifact" (broadening of septal edge at the margins of the defect) in improving specificity of echocardiographic diagnosis. Kececioglu-Draelos[108] demonstrated that actual VSD dimensions usually exceeded the measured VSD image in the 2-D echocardiogram. Other reports have demonstrated usefulness of 2-D echo for detection of left ventricle to right atrial shunts,[109,110] aneurysms of the ventricular septum,[111] aortic valve prolapse associated with VSD,[46] and assessment of the patient after VSD repair.[112] Recent work has led to revision of the nomenclature of ventricular septal defect based on echocardiographic as well as morphologic criteria.[15–17]

The evaluation of the child with ventricular septal defect by 2-D echocardiography requires a complete, segmental study including parasternal long axis, multiple parasternal short axis, apical and subcostal 4-chamber and suprasternal views. A complete examination is essential to provide accurate information about the presence, size, location, and number of septal defects, as well as the presence of associated lesions.

The standard parasternal long axis view demonstrates the outlet septum and most accurately demonstrates perimembranous or muscular outlet defects, particularly defects of the malalignment type.[15] Muscular trabecular defects are occasionally identified in this view, but perimembranous trabecular defects are generally not.[106] "Aneurysm" associated with perimembranous defects may often be visualized in the parasternal long-axis view.

Medial angulation of the transducer from the standard parasternal long axis view permits imaging of the tricuspid valve and a portion of the membranous septum. Perimembranous trabecular and perimembranous inlet defects will often be seen. Lateral angulation permits imaging of the right ventricular outflow tract and pulmonary valve, and doubly committed subarterial defects.[15,17]

Parasternal short axis views, with careful base-to-apex scanning, permits imaging of the entire ventricular septum and most ventricular septal defects (Fig. 59–6). When the septal and Moderator bands of the right ventricle can be identified, inlet and outlet defects are more easily classified.[15] Likewise, the medial papillary muscle of the tricuspid valve can help to distinguish defects in the outlet septum from those of the membranous septum. The former are located superior and to the left of that landmark, while the latter are positioned inferior and to the right.

Fig. 59–6. Parasternal short axis view, demonstrating a large perimembranous VSD.

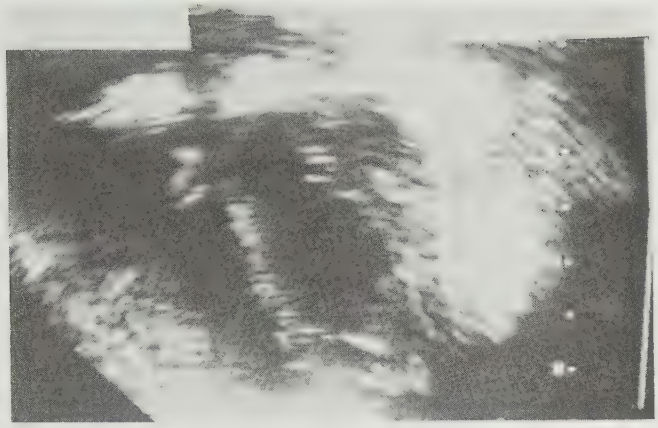

Fig. 59–7. Apical four-chamber view, demonstrating a small perimembranous VSD with ''aneurysm'' projecting toward the right ventricle.

Four-chamber views from the apical and subcostal positions best demonstrate muscular inlet and muscular trabecular defects, as well as most perimembranous defects (Figs. 59–7 and 59–8). They also best demonstrate atrioventricular valve morphology and help identify defects of the atrioventricular canal.

Contrast echocardiography has been used to enhance the sensitivity and amplify the assessment of VSD by both M-mode and 2-D techniques.[98] Serwer et al.[113] used contrast M-mode echo to help classify patients into four groups based on right ventricular pressure dynamics. Those with small VSD and normal right ventricular pressure had contrast injected from a peripheral vein appear to the right ventricle only. Those with moderate-size VSD and moderate right ventricular hypertension had appearance of contrast in the left ventricle during diastole, but none in the aorta. Those with large VSD and low resistance showed contrast in the left ventricle during diastole only, but also in the aorta. A single patient with large VSD and high resistance had a similar finding, with right-to-left shunting of contrast much earlier in diastole.

Two-dimensional echocardiography with contrast permits demonstration of left-to-right shunting by visualization of ''negative'' contrast jets. This may occasionally enhance the sensitivity of 2-D echo in detection of ventricular septal defect.[114,115] Demonstration of right-to-left shunting of contrast on 2-D echocardiography is strongly suggestive of right ventricular hypertension.

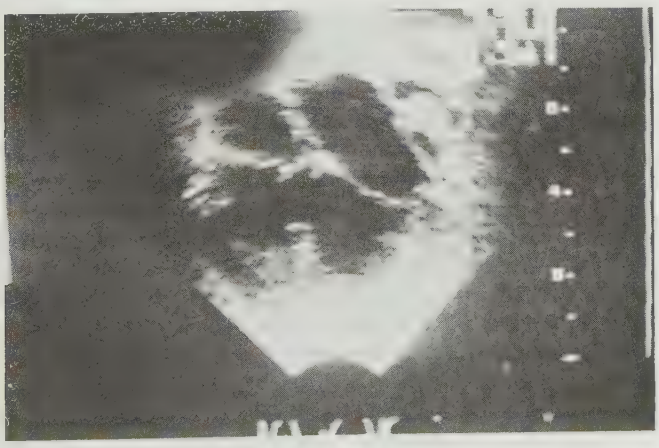

Fig. 59–8. Apical four-chamber view demonstrating a large perimembranous VSD. The tricuspid valve is closed, but the tricuspid valve annulus appears to override the defect.

Doppler echocardiography has been a helpful adjunct for enhancing the sensitivity/specificity of conventional imaging echocardiography in detection of ventricular septal defects. It is becoming a powerful modality for assessing hemodynamics as well. Stevenson[116,117] used pulsed Doppler in conjunction with M-mode echocardiography to identify left-ventricle–to–right-ventricle jets, localize defects, and distinguish VSD from mitral regurgitation. He also demonstrated the value of the pulsed Doppler evaluation when performed in conjunction with the 2-D echocardiogram.[118] The current 2-D echocardiographic examination, as described above, is ordinarily accompanied by pulsed Doppler interrogation of the imaged ventricular septum,[119,120] with confirmation of flow through actual defects, and its absence at the site of imaging artifacts.

Pulsed Doppler has also been used to assess cardiac output by combining flow velocity measured with imaged valve area.[121] This technique has been adapted to patients with VSD as well as other left-to-right shunts in the noninvasive assessment of pulmonary-to-systemic flow ratio.[122] Continuous-wave Doppler echocardiography, more useful in the accurate quantitation of flow velocity, recently has been applied to the assessment of pulmonary artery pressure. Continuous-wave Doppler measurement of flow velocity across a defect itself reliably correlates with left-ventricle–to–right-ventricle pressure gradients.[123,124] Continuous-wave Doppler measurement of regurgitant flow velocity in patients with mild tricuspid regurgitation has also been used to estimate right-ventricle–to–right-atrium pressure gradients and identify patients with significant right ventricular hypertension.

Color-flow Doppler imaging, a relatively new technique, has begun to enhance the sensitivity of the Doppler/2-dimensional echocardiographic assessment of the child with congenital heart disease.[125] Color-flow imaging of VSD flow has been demonstrated to be a sensitive and reliable finding.[125–128] Its utility in assessment of this defect presently lies in improved detection of small areas of left-to-right flow in small, difficult-to-image, defects.[125,126]

Ultrasound examination has become an essential part of the noninvasive assessment of the child with suspected or known ventricular septal defect. All children with symptomatic ventricular septal defect, and all children in whom surgical repair of ventricular septal defect is planned, should undergo a complete 2-D echocardiographic and Doppler examination. It is the most powerful noninvasive tool presently available for assessment of the presence, number, size and location of ventricular septal defects—as well as the presence of associated lesions. In addition, all children over the age of 2 years whose ventricular septal defect has not closed spontaneously should undergo complete 2-D echocardiogram and Doppler evaluation. Doubly committed subarterial defects, which may predispose to the later development of aortic regurgitation,[36] and small malalignment defects, which may be associated with left ventricular outflow tract obstruction,[39] can hence be identified.

Limitations of the echocardiographic examination are not to be overlooked. Very small defects, those often confused with functional murmurs, may elude detection by even meticulous 2-D echocardiography and pulsed Doppler interrogation. Color-flow

imaged Doppler may help alleviate this problem. More important is the considerable technical skill required to perform a "complete" echocardiographic examination and the inherent dependence on the skill and diligence of the echocardiographer. Finally, while real-time 2-D imaging technology has maximized the noninvasive evaluation of VSD anatomy, the Doppler echocardiographic evaluation of hemodynamics has developed more gradually and has not, as yet, replaced invasive hemodynamic assessment of these patients.

OTHER NONINVASIVE STUDIES

Several other noninvasive techniques may be employed in the assessment of the child with ventricular septal defect. Unlike echocardiography, which has become quite standard in most institutions, their frequency of utilization varies widely from center to center.

Radionuclide studies in children have been available since the early 1970s.[129,133] These studies provide sensitive detection of left-to-right shunts, and are more accurate in the quantitation of pulmonary-to-systemic flow ratios when compared to the Fick method than is echocardiography.[129] Radionuclide studies also provide useful information about left and right ventricular function.[134] They have the disadvantage of providing minimal anatomic information. Moreover, nuclear studies are not completely "noninvasive" and the requirement for a timely bolus intravenous injection can be a significant disadvantage in infants.

Gated magnetic resonance imaging studies, as yet available in only a few centers, appear to be capable of providing excellent anatomic information about ventricular septal defect, as well as other cardiac malformations.[135,136] The data collected are static, but image quality is comparable to current echocardiography. Presently this technique is of limited value in infants, however, both because of limited resolution and the long data acquisition time.[136]

Computerized tomography has not generally been helpful in assessment of cardiac anatomy because of heart motion. The newer technique of cine computerized tomography may be valuable, but is only beginning to be applied to small children with congenital heart disease.

Pulmonary input impedance studies have been applied to experimental animals,[137] as well as children,[138] as an indicator of pulmonary vascular resistance, but have not yet found widespread clinical use.

CARDIAC CATHETERIZATION

Cardiac catheterization, usually performed in conjunction with selective cineangiocardiography, can provide accurate and valuable information about the child with ventricular septal defect. This includes confirmation of the defect, information about size and location of defects, the presence of associated defects, the magnitude of the left-to-right shunt, the pulmonary artery pressure and resistance, and the responses of either the resistance or shunt to acute pharmacologic intervention. With the noninvasive technology that is available at the present time, careful consideration must be given to selection of patients for catheterization based on specific unanswered and necessary questions. Previous authors have advocated cardiac catheterization for all infants with congestive heart failure,[19,71] for all patients in whom surgical repair of VSD is contemplated, and for all children in whom there is a question of elevated pulmonary artery pressure. Current practice in most institutions is somewhat more selective as to which patients undergo cardiac catheterization. Infants with small defects, and asymptomatic infants under 6 months of age with larger defects, are not usually catheterized. Symptomatic infants (as well as asymptomatic infants suspected of having a moderate or large defect) undergo a careful 2-D echocardiogram and Doppler study. If that study discloses simple ventricular septal defect, medical management of symptoms (see below) is undertaken. If the echocardiogram is not definitive for a diagnosis of simple VSD, or cannot adequately exclude associated lesions, then cardiac catheterization is performed. If medical therapy is unsuccessful and intracardiac repair is contemplated, cardiac catheterization is usually undertaken. At our institution, we routinely perform cardiac catheterization and cineangiography prior to intracardiac repair of all ventricular septal defects, although other centers are now referring patients for intracardiac repair without invasive study.[17]

Infants whose symptoms are alleviated with medical therapy and those whose noninvasive studies suggest a defect that is not small are routinely catheterized in our institution before 1 year of age. Older children undergo catheterization if there is suspicion of persistent significant left-to-right shunt or elevation of pulmonary artery resistance. Increasing reliance of many centers on Doppler echocardiographic estimates of pulmonary-to-systemic flow ratios and pulmonary artery pressure will tend to decrease the future number of children catheterized in this category.

Techniques of right and left heart catheterization are well described elsewhere in this text and by others.[71,139–141] Complete right heart catheterization should be performed, including measurement of mean and phasic pulmonary artery wedge pressures, and pressures in the pulmonary branches, pulmonary trunk, right ventricle, and right atrium. Accurate blood oxygen saturations should be determined in the pulmonary arteries, pulmonary trunk, right ventricle, right atrium, superior and inferior vena cavae. Oxygen consumption should be measured using the flow-through or Douglas bag techniques to facilitate calculation of actual pulmonary blood flow and pulmonary vascular and systemic arterial resistances.[71]

We routinely employ continuous femoral arterial pressure monitoring during catheterization of the child with ventricular septal defect. Left heart study and ventriculography are included in the catheterization protocol of these infants as well. These may often be performed through a patent foramen ovale. Otherwise, the retrograde arterial or transseptal approach is utilized.

Determination of systemic-to-pulmonary flow ratio is made using the Fick principle and comparison of systemic arterial oxygen saturation with pulmonary and mixed venous oxygen saturation. This ratio is adequate for the assessment of flow in the presence of normal pulmonary artery pressure, and hence low pulmonary artery resistance. If pulmonary artery pressure is elevated (mean pulmonary artery pressure equal to one-half mean systemic pressure or greater), oxygen consumption should be measured to permit calculation of actual pulmonary blood flow and pulmonary resistance. Care must be taken in this instance to exclude anomalies of left ventricular inflow which might exacerbate pulmonary hypertension.

When pulmonary vascular resistance is significantly elevated (Rp/Rs ratio >0.3), reactivity of the pulmonary arterial tree is

ordinarily assessed by administration of oxygen.[71] Oxygen is delivered in a concentration of 0.95 to 1.0 via headbox for 5 minutes, and repeat measurements of pulmonary and systemic pressures and pulmonary arterial, systemic arterial, and mixed venous oxygen content are repeated. Systemic and pulmonary arterial blood gas determinations are also essential to assess adequacy of ventilation, and include dissolved oxygen estimation into the calculation of pulmonary and systemic blood flows. If elevated pulmonary vascular resistance is unresponsive to oxygen, further assessment of reactivity should be made by the administration of tolazoline, 1 mg/kg[71] or isoproterenol, 0.05 mg/kg/min.[142] It should be mentioned that some laboratories do not routinely employ techniques for assessment of pulmonary vascular reactivity, feeling that resistance under measured baseline conditions alone is the best indicator of operative survival.[143]

Cineangiography

Cineangiographic evaluation in the child with ventricular septal defect should be carefully designed to identify associated conditions and define the precise anatomy of the defect itself. Right ventriculography or pulmonary arteriography may be indicated, especially the latter in instances where pulmonary vein stenosis, cor triatriatum, or mitral valve abnormality is a suspected cause of pulmonary hypertension. Some centers frequently employ magnification pulmonary wedging angiography[144] as part of their evaluation of the child with pulmonary vascular obstructive disease. Pulmonary arteriography with left heart follow-through is inadequate for visualization of the precise anatomy of ventricular septal defect.

Selective cineangiography of the aortic root may be indicated in instances of outlet VSD with aortic valve prolapse or aortic regurgitation.[47] Aortography may also be necessary to evaluate the contribution of patent ductus arteriosus to a large left-to-right shunt in the infant.

Demonstration of the VSD demands selective left ventriculography, preferably with biplane projections. Ideal visualization of the defect requires alignment of the plane of the defect parallel to the x-ray beam. The curvilinear and helical configuration of the septum occasionally makes this difficult, but 2-dimensional echocardiography has become a boon to the angiographer by helping to localize the defect prior to catheterization, thus minimizing the number of injections required. Optimal visualization is achieved with 1.5 to 2.0 ml of 75% contrast per kilogram of body weight,[34] delivered in no more than one second.

The concept of axial cineangiography described by Bargeron,[14] and used by most centers today, finds no better application than in the demonstration of defects of the ventricular septum.[14,29,34,145–147] Angulation can be achieved by maneuvering of the patient's position with conventional angiographic equipment, or angling of the tube and image intensifier with newer equipment.

Defects of the perimembranous septum are usually well demonstrated with a steep left anterior oblique (LAO) projection (75°), with cranial angulation of 20°[29,34] (Fig. 59–9). Doubly committed subarterial defects may also be visualized in this view, or occasionally with a steep right anterior oblique projection.[29,34] This combination of projections is also effective for demonstration of perimembranous defects with left-ventricle–to–right-atrial shunting.[147]

Posterior defects, those of the perimembranous or muscular inlet septum, may appear to lie in the midmuscular septum of the LAO projection.[34] They are best demonstrated in the four-chamber view (45° cranial and 20° left anterior oblique).[34,145] Defects of the muscular trabecular septum, often multiple, are usually identified in the cranially angulated long-axial oblique view (Fig. 59–10), and its biplane counterpart, the steep right anterior oblique projection. Occasionally, the four-chamber view may also be useful, however, to demonstrate additional defects.[34,146]

Fig. 59–9. Left ventriculogram taken in the steep LAO; cranial projection, demonstrating a small perimembranous VSD.

NATURAL HISTORY AND CLINICAL COURSE

Management decisions for patients with ventricular septal defect depend, as with most conditions, on a knowledge of the natural history of the defect. Such information is, of course, not entirely available, since longitudinal patient followup entails some degree of patient management. A number of investigators have reported the clinical course and outcome of large cohorts of children with VSD.[16,20–23,56,57,148,152] These reports vary in their patient substrate and the extent to which they reflect "natural history" as opposed to clinical outcome. Nonetheless, taken in conjunction with other observations and numerous smaller studies, they provide several general conclusions which form the basis for current management (Table 59–1).

A substantial portion of patients with ventricular septal defect have a small defect. This is especially true if the diagnosis is made

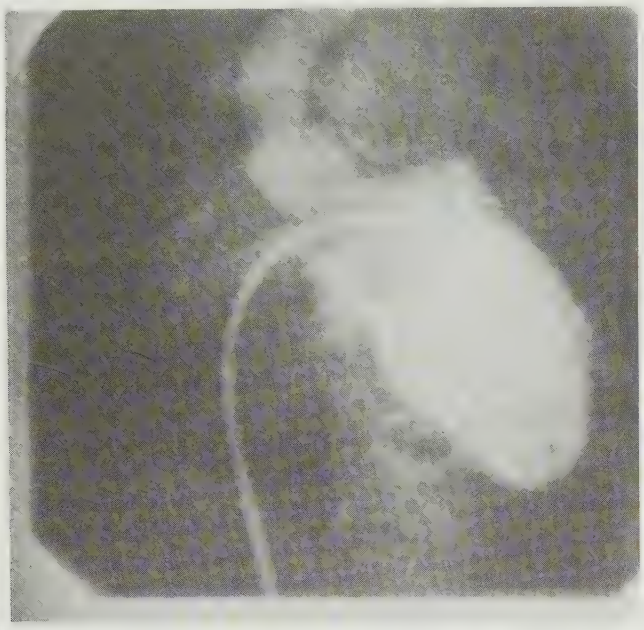

Fig. 59–10. Left ventriculogram taken in the steep LAO; cranial projection, demonstrating three small defects in the muscular trabecular septum.

only on the basis of a murmur[16,23] and if the diagnosis is made in patients who present late.[56] However, even if patient selection is restricted to infants,[149] or to patients studied invasively,[22,56] a number of patients will have a small defect.

Many small defects close spontaneously—with estimates ranging from 9%[56] to 75%,[152] depending on patients evaluated—but with an actual number probably exceeding 35%.[16,20,21,23,149,153] While this figure reflects the rate of spontaneous closure for perimembranous trabecular defects, the incidence is higher for defects of the muscular trabecular septum[152] and perimembranous inlet septum,[16] whereas spontaneous closure of defects of the outlet septum is probably rare.[16] Closure most commonly occurs prior to 2 years of age,[22,152] but may occur later in childhood,[23,56,149,152] and has been reported in adults.[154] Regardless of closure, patients with small defects do well and do not require surgical intervention. Whether they are judged "small" by hemodynamic (normal pulmonary artery pressure, pulmonary-systemic flow ratio less than 2:1) or clinical criteria (normal pulmonic closure sound, minimal abnormal radiographic findings, minimal left ventricular hypertrophy, and no right ventricular hypertrophy by electrocardiogram), there is no indication that these patients have significant functional impairment in childhood or limited longevity. There is likewise no evidence that pulmonary vascular resistance increases later.[56] Adults with small VSD may have subclinical compromise of cardiac "reserve," but, as yet, the relevance of this observation to the management of children with VSD is unclear.[155] There is some tendency for moderate and large defects to close spontaneously as well, though this is less frequent than with small defects.[22,23,56] The natural history study reported in 1977 found an 8% rate of spontaneous closure of large defects by 2 years of age. Those defects that do not close may reduce in size with time.[56]

Pulmonary vascular resistance must also be considered. Moderately elevated resistance (pulmonary-systemic resistance ratio <0.5) tends not to increase during infancy, but may worsen (or may improve) later during childhood.[56] Severely elevated resistance seldom improves, and significant pulmonary vascular obstructive disease may develop as early as the second year of life.[19,22,56,156–158]

Most infants with moderate-size defects who present with congestive heart failure can be managed medically[19,22,56] (see below), as can a number of infants with large defects. The advantage of conservative therapy over surgery in VSD is the tendency for these defects to become smaller or to close, potentially obviating the need for surgery altogether. Infants whose congestive heart failure cannot be controlled are generally referred for surgical repair. Certain infants are known to be at higher risk for uncontrollable congestive heart failure. These include infants born prematurely or with low birth weight, infants with chromosomal defects, and those with major extracardiac anomalies.[23,56,159] These infants are known to be at high risk for surgical mortality as well.

Table 59–1. Clinical Course of Children with Isolated VSD

1. Many have small defects
2. Children with small defects do well
3. Small defects frequently close
4. Large defects may close and often become smaller
5. Modest elevation of pulmonary vascular resistance does not progress in the first year of life
6. Severe elevation of resistance may progress early
7. Most infants with congestive heart failure can be managed medically
8. Some infants are considered "high risk"

MEDICAL THERAPY

Infants

The medical treatment of infants with ventricular septal defect is directed at the control of congestive heart failure. The goal of therapy is the relief of symptoms, minimization of frequency and severity of respiratory infections, and normal growth.

Infants with a large defect may manifest severe congestive heart failure at the time of their initial diagnosis. These infants should be hospitalized for initial management, which should include fluid restriction (usually 60 to 80 ml/kg/day), alleviation of temperature stress by careful attention to a normothermic environment, and gentle handling to minimize physical exertion. Occasionally mild sedation (morphine, 0.05 mg/kg) will relieve some of the metabolic expenditure of the irritable infant. It may initially be difficult to differentiate bacterial pneumonia superimposed upon congestive heart failure. In that instance, blood and possibly tracheal cultures should be obtained, and broad-spectrum antibiotic therapy provided until infection is excluded. Severe pulmonary edema may be associated with hypoxemia and supplemental oxygen may be required. It must be kept in mind, however, that oxygen is a pulmonary vasodilator, which may decrease pulmonary vascular resistance, increase left-to-right shunting, and exacerbate congestive heart failure. Oxygen should be used judiciously only to relieve hypoxemia, demonstrated by blood gas determination or noninvasive oximetry. Increased respiratory effort without hypoxemia is best treated by other means. Severe respiratory distress should be treated with endotracheal intubation and continuous

positive airway pressure, with or without mechanical ventilation. The benefit of positive end-pressure and mechanical ventilation in the early stabilization of severely ill infants can be dramatic.

Diuretic therapy should be instituted promptly for the infant with congestive heart failure. Furosemide or ethacrynic acid given intravenously two or three times daily is usually effective.

Digoxin has long been part of the conventional management of infants and children with symptoms of congestive heart failure due to left-to-right shunt.[18,19,160] Hospitalized children are usually given a loading dose over 24 hours, and then continued on maintenance therapy. While the inotropic effect of cardiac glycosides on the immature myocardium has been questioned,[161–163] studies[163] and clinical experience[18,19,160] attest to the beneficial effect of digoxin in some, if not all, infants with ventricular septal defect. Other inotropic agents generally are not required in the management of isolated ventricular septal defect.

Considerable interest has been directed at the utility of systemic afterload reduction for VSD.[163,164,166–168] In acute congestive heart failure, secondary to left-to-right shunting, hydralazine appears to improve pulmonary-to-systemic flow ratios in those patients with measured elevation of systemic resistance.[166–168] Nitroprusside may be less effective or even detrimental,[165] while studies in dogs suggest that prazosin may be more effective.[164] As yet, the effect of chronic use of afterload reducing agents for patients with ventricular septal defects remains to be demonstrated.

Infants who present earlier, or with less severe manifestations of congestive heart failure, may often be treated at home. Oral digoxin therapy may be instituted in a maintenance dose, with anticipated achievement of steady-state serum concentration in 4 to 7 days. Diuretic therapy consists of furosemide, ethacrynic acid, or hydrodiuril given two or three times daily. Potassium wasting with each of these effective agents may warrant addition of spironolactone and/or oral supplemental potassium replacement. In occasional patients, oral hydralazine therapy may be added to the pharmacologic regimen, but, as mentioned, the long-term benefit has not been documented.

Poor weight gain in the presence of congestive heart failure is due to the combined effects of increased metabolic expenditure and poor caloric intake.[159] Pharmacologic therapy helps decrease abnormal respiratory effort, decreasing caloric utilization and improving intake. Poor weight gain may still be a problem, however, and failure to thrive has commonly been the indication for early repair of ventricular septal defect. Caloric supplementation by the addition of carbohydrate and medium-chain triglyceride preparations to conventional formulas may improve weight gain. In recent years, the use of home nasogastric tubes for bolus, nighttime, or continuous drip feedings, has become a possible method of improving caloric intake and achieving acceptable weight gain.[169] Clearly, the dietitian has become an essential member of the cardiology team caring for these infants.

Older Children

Older children with ventricular septal defect are seldom symptomatic and require little in the way of medical therapy. Children with significant left-to-right shunts or elevated pulmonary artery pressure generally undergo surgical repair. Medical followup in the older age groups then consists of periodic evaluation, encouragement of full activity, and education about the proper use of antibiotic prophylaxis for bacterial endocarditis.

Patients with ventricular septal defect and pulmonary vascular obstructive disease who are deemed "inoperable" because of irreversibly elevated resistance (see below) require more intensive support and symptomatic therapy as cyanosis progresses and activity becomes more limited. While specific drug therapy of the vascular obstructive disease itself is not available, some centers are using antiplatelet agents, such as aspirin or dipyridamole, in an effort to retard the progression of the disease process. Improvement in the symptoms associated with polycythemia of Eisenmenger's complex—headache, extreme fatigue, and extreme dyspnea—may be provided by partial exchange transfusion for red cell volume reduction.[170] There is no evidence that the symptomatic therapy has any beneficial effect on the mortality rate or life expectancy with this condition.

SURGICAL THERAPY

Since Lillehei's early report of successful closure of ventricular septal defect using the cross-circulation technique,[8] the surgical approach to the condition has been the subject of numerous publications.[171–186] Attention is focused on questions of palliative versus definitive surgery, indications for surgery, surgical techniques, and surgical results.

Palliative surgery for left-to-right shunts with congestive heart failure was recommended by Muller[7] in 1952 and was popular in the 1960s as part of a two-stage repair of ventricular septal defect.[185,187] Disadvantages of pulmonary artery banding are numerous[176,188] and include early operative mortality, persistent congestive heart failure after banding, technical difficulty with debanding at the time of second-stage repair, development of subaortic stenosis, and overall combined mortality of the two-staged repair. Improved techniques and operative survival, even for small infants, with definitive repair[178,179,181,183–186,188] has rendered the two-stage approach for simple VSD obsolete in most centers.[173,176,188] Pulmonary artery banding remains useful in certain "high risk" patients (multiple VSDs, extremely small patients, those with concomitant lung disease)[179,181,189] and for certain patients with associated conditions (coarctation of the aorta, interrupted aortic arch),[186] but for the majority of patients with simple VSD who require operative intervention, primary intracardiac repair is the procedure of choice.[179,188]

Indications for surgical repair of ventricular septal defect were developed in the decade after Lillehei's initial surgical report,[171] but have not changed a great deal since the mid-1960s.[19,172,188,189] Early experience demonstrated the high risk associated with repair of larger VSD with severe pulmonary vascular obstructive disease.[10,190,192] At the same time, consideration of the natural history of small defects and their benign course led to a minimum left-to-right shunt size as an indication for surgery.[19,172,186] Current indications for surgery are reasonably standard[19,172,185,186,189] (Table 59–2). Surgical repair in infancy is undertaken for control of intractable congestive heart failure, including recurrent lower respiratory tract infections or growth failure. Patients with large defects whose congestive heart failure is controlled but whose pulmonary artery pressure remains elevated (>½ systemic) are repaired prior to 2 years of age,[156–158] or, in many centers, before 1 year of age. Older children undergo surgical correction if pulmonary-to-systemic flow ratio is >2:1[19,186] or, in some centers,[18] >1.5:1. Pulmonary arteriolar resistance equal to systemic resis-

Table 59–2. Surgical Repair of Ventricular Septal Defect

Age	*Indications**
Under 6 months	Uncontrolled congestive heart failure
6 to 24 months	Pulmonary hypertension or symptoms
Over 24 months	$Q_p/Q_s > 2/1$
*Contraindications	
Absolute	$R_p/R_s > 1/1$ or $R_p > 12$ Wood units
Relative	$R_p/R_s > 0.75/1$ or $R_p > 8$ Wood units

tance, or pulmonary arteriolar resistance greater than 12 Wood units,[10] is regarded as a contraindication to surgery. Pulmonary-to-systemic resistance ratio between 0.5 and 1.0, or pulmonary arteriolar resistance between 8 and 12 Wood units, is generally felt to substantially increase the risk of surgical correction and unfavorably affect long-term prognosis.[158] These patients usually undergo further evaluation with provocative testing in the catheterization laboratory,[71,142–144,192–194] pulmonary wedge angiography,[144] or lung biopsy[193,194] to elucidate the severity of pulmonary vascular disease prior to surgical correction.

The technical aspects of surgical repair of VSD are well described.[172,175,176,180–186,195–198] The majority of perimembranous defects may be closed by a transatrial approach,[173,182,184,186] although many surgeons prefer a right ventriculotomy.[176] Defects of the inlet septum may occasionally require detachment of the septal leaflet of the tricuspid valve for exposure.[196] Defects of the muscular trabecular septum, particularly when multiple, are often best approached through a left ventriculotomy.[175,197] Results with this approach suggest that the improved visualization of multiple defects from the left ventricular aspect offsets the potential compromise of left ventricular function.[175,197] Nonetheless, many surgeons prefer not to perform incisions in the systemic ventricle. Defects of the outlet septum are best approached through a ventriculotomy, or through the pulmonary artery.[195] The technique of profound hypothermia and circulatory arrest[173,176,184,198] is employed by many centers for VSD repair in infants less than 1 year of age, while most centers employ conventional cardiopulmonary bypass for older infants and children.

Intracardiac repair of ventricular septal defect can be accomplished with reasonable safety. Early operative mortality rates range from 1 to 2% for uncomplicated defects in older children.[182,186] In infants under 1 year, operative mortality rates range from 2%[184] to 13%,[188] with most series reporting mortality <10%.[176–179,183] Earlier reports with pulmonary artery banding suggested an in-hospital mortality associated with that procedure in the range of 13%.[188] The New England Regional Infant Cardiac Program found an overall mortality rate of 44% for infants undergoing primary VSD repair.[149] It is misleading to compare these figures because of differences in time frame, patients included in the study, and number of centers involved. It is clear, however, that at the present time, repair of uncomplicated VSD in the older child carries a low operative risk. The operative mortality in small infants is substantially higher, but remains less than 10%.[177] This mortality is apparently lower than the overall mortality associated with two-stage repair in the same group of infants.

Postoperative Management

The potential postoperative problems directly related to intracardiac repair of ventricular septal defect include residual left-to-right shunt, elevated pulmonary artery pressure, ventricular dysfunction, and surgical atrio-ventricular block. Distinguishing between the first three may occasionally be difficult in the post-surgical intensive care unit, but it is critical for the determination of appropriate therapy.

Residual left-to-right shunt after repair of VSD may occur in 14 to 30% of cases,[56,177,183,185] and may be hemodynamically significant in up to 10%.[183] Its clinical detection is confounded by a high prevalence of murmurs in the immediate postoperative period. In some centers, pulmonary artery catheters are routinely used for postoperative assessment,[199] and elevated pulmonary artery blood oxygen saturation can be used to detect significant left-to-right shunting.[199] Echocardiography with pulsed Doppler can also be adapted to the detection of residual defects. Patients with persistent cardiomegaly and evident low cardiac output in the early postoperative period should undergo noninvasive evaluation and, often, early postoperative cardiac catheterization. The presence of a residual left-to-right shunt with pulmonary-to-systemic flow ratio of >1.5:1 with evident compromise of cardiac output should be considered as a likely indication for reoperation.

Patients with preoperative pulmonary hypertension may have elevated pulmonary vascular resistance in the postoperative period and exhibit reduced cardiac output and right heart failure. Residual left-to-right shunt must be excluded. Noninvasive estimation of pulmonary artery pressure is difficult in the early postoperative period. Routine use of pulmonary artery catheters[199] or their use in patients known preoperatively to have elevated pulmonary vascular resistance may be helpful in identifying this condition, as well as assessing the response to therapy. Alleviation of the elevated resistance may be challenging. Maintenance of normal arterial P_{CO_2} and P_{O_2} by aggressive, and occasionally prolonged, mechanical ventilation may avert the pulmonary vasoconstriction associated with hypoventilation and hypoxemia. Hyperventilation is probably less effective, and hyperoxygenation (P_{O_2} >120 mm Hg) may be of no benefit. Pharmacologic agents that may be useful as pulmonary vasodilators include tolazoline, isoproterenol, nitroprusside,[200] and nitroglycerin. Each must be used carefully and with appropriate monitoring to assess efficacy. Extracorporeal membrane oxygenation has been used successfully for a patient with postoperative pulmonary hypertension unresponsive to conventional treatment.[201] An essential part of the management of postoperative pulmonary hypertension is patience, as the recovery period is often prolonged despite optimal therapy.

Patients may exhibit poor cardiac output in the postoperative period in the absence of residual shunt or elevated pulmonary vascular resistance. Certain subsets of patients may be particularly predisposed to myocardial dysfunction postoperatively. These include patients with very large preoperative shunts[202] and patients with long-standing left ventricular volume overload.[203,204] These patients are treated with inotropic agents and afterload reduction when necessary. Occasionally, longterm anti-congestive therapy is required.

Surgical complete atrio-ventricular block has been a relatively unusual complication of intracardiac repair of VSD since the early 1960's.[172,205,206] In most centers, the incidence is less than 2% with simple VSD.[180] Transient AV block may occasionally occur and is managed with temporary cardiac pacing. Insertion of a permanent pacemaker is generally deferred for 1 to 2 weeks to allow resolution of transient block.[207] Right bundle branch block is ex-

tremely common following VSD surgery and has not yet been associated with adverse effects.[97,208]

Longterm Results

Longterm outcome of patients following repair of ventricular septal defect is largely dependent on age and hemodynamic status at the time of repair. Follow-up catheterization studies have demonstrated normal pulmonary vascular resistance in most children repaired before 2 years of age.[56,158,172,191] Children undergoing surgery later may have a less predictable fall in pulmonary vascular resistance. Patients with normal resistance at the time of surgery do not experience a subsequent rise in resistance, but in certain of the patients with moderately elevated resistance who are repaired later, the pulmonary vascular resistance increases.[56,158,209,210] This increase in resistance is neither as uniform nor as marked, however, as with similar patients in whom surgery is not performed.[211] While the majority of patients surviving repair of VSD are asymptomatic,[56,212–214] Maron, et al., [214] found abnormal responses to exercise in nearly half of a group of patients studied 3 to 15 years postoperatively. Jarmakani, et al.,[215] found decreased left ventricular performance in a group of patients repaired at a mean age of 5 years. A subsequent study[203] disclosed better residual left ventricular performance in patients repaired before 1 year of age.

Late death, according to the National History Study in 1977, occurred in 10 of 126 infants and 7 of 259 older children who underwent surgical correction.[56] Others report similar incidence of late death.[211,216] The most common form of late death was "sudden death."[56] This may not necessarily imply sudden "unexpected" death, in that certain patients are at greater risk of sudden death by virtue of elevated pulmonary artery pressure,[213] or malignant arrhythmias.[216]

Patients with small defects who do not undergo surgical repair are generally asymptomatic.[56,217] While there may be subtle abnormalities of myocardial performance associated with chronic mild left ventricular volume overload,[218] these patients rarely manifest clinical deterioration,[217] and there is some evidence that they may benefit from dynamic exercise.[80] Late sudden deaths have not yet been reported in this group.[217,219]

Patients with large VSD and pulmonary vascular disease who are deemed "inoperable" generally undergo hemodynamic and clinical deterioration during the second and third decades of life, and most die before age 40,[10,19] although survival to age 63 has been reported.[220] Death is usually due to pneumonia, pulmonary hemorrhage, progression of right heart failure, or a sudden event (probably an arrhythmia).

ENDOCARDITIS, PREGNANCY, AND INSURABILITY

Infectious endocarditis is a well-known, and not uncommon, complication of ventricular septal defect.[221] Incidence estimates range from less than 1%[23] to 15%.[219,222] Surgical repair without residual defect reduces this risk substantially,[221] but residual defect after intracardiac repair appears to present the same or greater[222] risk for development of endocarditis as unoperated defects. At the present time, antibacterial prophylaxis for prevention of endocarditis is recommended for all children with ventricular septal defect, whether surgically repaired or not.

Small ventricular septal defect with good functional status does not increase maternal risk in pregnancy.[223] Patients with a large defect, or a postoperative defect with less-than-excellent clinical status, have a substantial likelihood of cardiac-related symptoms (angina or congestive heart failure) during pregnancy, although maternal death is rare. Mothers with ventricular septal defect have an increased incidence of spontaneous abortion,[223] and an apparent incidence of congenital heart disease in their offspring of approximately 21%.[223] This figure is substantially higher than earlier predictions based on the multifactorial inheritance model.[224]

Life insurance guidelines for patients with congenital heart disease have been outlined by the American Heart Association Council of Cardiovascular Disease in the Young.[225] Patients with small VSD are felt to have standard insurance risk. Moderate VSD, with cardiomegaly, increased pulmonary blood flow, and normal pulmonary vascular resistance, have minimum-to-moderate substandard insurance risk. Patients with large VSD are probably uninsurable. Patients who undergo repair of ventricular septal and have no residual defect or pulmonary hypertension have standard risk. Those with residual defects have moderate substandard risk. Those with pulmonary hypertension postoperatively are probably uninsurable.

GUIDELINES FOR MANAGEMENT

Based on the above considerations, we have established guidelines for the management of children with ventricular septal defect (Table 59–3). Their application to a particular patient is, of course, dependent upon the clinical circumstances and variation from center to center.

Infants with findings suggestive of ventricular septal defect must be carefully assessed for evidence of congestive heart failure and for the presence of associated lesions. The infant should be followed closely over the first 6 months of life, during which time falling pulmonary vascular resistance may cause an increase in left-to-right shunting. Many small defects will close spontaneously. Most pediatric cardiac centers do not continue to follow those patients. Children over 2 years of age whose defects have not closed spontaneously should undergo 2-D echocardiography to exclude left ventricular outflow tract obstruction and subarterial defect, which might predispose to aortic regurgitation. Patients with small defects generally then are followed periodically for overall assessment and re-emphasis of the need for bacterial endocarditis prophylaxis.

Infants with evidence of congestive heart failure should undergo invasive or noninvasive anatomic assessment. If congestive heart failure does not respond to medical therapy, complete repair is the preferred surgical treatment. If failure responds to medical therapy, including a satisfactory rate of growth, the infants await hemodynamic assessment (usually by cardiac catheterization) later in the first year of life. If pulmonary artery resistance is elevated, intracardiac repair is performed electively between 1 and 2 years of age. Children in whom pulmonary vascular resistance is not elevated, but in whom there is significant, persistent left-to-right shunting, usually undergo intracardiac repair prior to starting school, or earlier in many centers.

Following intracardiac repair, all children should have periodic evaluation by a cardiologist and continued endocarditis prophylaxis.

Table 59–3. Guidelines for Management

Age	*Echocardiography*	*Cardiac Catheterization*	*Surgery*
Under 6 months	1. Symptoms 2. Questionable findings 3. Associated conditions	1. Ambiguous echo findings 2. Preoperative	1. Uncontrolled congestive heart failure
6 to 24 months	1. Symptoms 2. Pulmonary hypertension 3. Associated conditions	1. Preoperative 2. Pulmonary hypertension	1. Pulmonary hypertension 2. Symptoms (or medications)
2 to 5 years	1. Associated conditions 2. Location of VSD	1. Preoperative	1. $Q_p/Q_s > 2/1$
Over 5 years	1. Location of VSD		

THE FUTURE

The trend for an improved outlook for these patients will doubtless continue over the next decade. A closer look at the "high-risk" patient group and further progress in the management of heart failure will hopefully permit even better patient selection and improved condition of patients referred to the operating room. Anatomic and hemodynamic data are becoming increasingly available without the need for catheterization. It is likely that diagnostic catheterization and angiocardiography, even for preoperative assessment, will become the exception. At the same time, interventional catheterization has become a reality for several other lesions and the catheter closure of ventricular septal defect is appealing. As yet, this procedure remains investigational, but may well become clinically useful for closure of muscular, and perhaps perimembranous, defects.[226]

Pulmonary vascular disease remains an area of unsolved problems. Early surgical correction of patients with elevated resistance has helped prevent the disease in many patients, but has not eliminated the condition entirely. Definitive therapy for patients with established pulmonary vascular disease does not seem likely in the near future, but improved medical palliative therapy may retard its progression, and heart-lung transplantation will become a more viable therapeutic option for some. Further investigation into the etiology of vascular disease itself, however, is most promising of all, as it can be applied to improved early identification of patients at risk for pulmonary vascular disease and possibly its early prevention.

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CHAPTER 60

Defects of the Atrial Septum Including the Atrioventricular Canal

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Congenital defects of the atrial septum are common. They may be located in different anatomic portions of the atrial septum; the location of the defect generally reflects the abnormality of embryogenesis that led to the anomaly.[1,2] Atrial septal defects may be only cardiac anomalies or they may be associated with other congenital cardiac abnormalities. The size may vary greatly. The functional consequences of defects of the atrial septum are related to the anatomic location of the defect, the size of the defect, and the presence or absence of other cardiac anomalies.[3–7]

Developmental abnormalities resulting from improper partitioning of the embryologic atrioventricular canal often lead to a communication between the right and left atria. Accordingly, the spectrum of defects comprising the group of atrioventricular canal anomalies is considered in this chapter, but as a separate section. Generally, all atrioventricular canal (endocardial cushion) defects that have an intra-atrial communication also have major abnormalities of the atrioventricular valves and the ventricular septum.

HISTORICAL ASPECTS

Galen knew that an interatrial communication existed in the normal fetus.[8] da Vinci described an atrial septal defect in a human autopsy specimen, illustrating his findings.[9] von Rokitansky gave complete pathological descriptions of atrial septal defects.[10] Roesler[11] described the findings at autopsy of 62 patients with atrial septal defects, one of which had had the diagnosis of atrial septal defect made during life. With increasing clinical awareness of the symptoms and signs accompanying atrial septal defects the clinical diagnosis was made more frequently. Bedford and coworkers[12] made the diagnosis of atrial septal defect in 53 patients, 10 of whom had the diagnosis confirmed by subsequent autopsy. The clinical application of cardiac catheterization beginning in the late 1940s made possible confirmation of the clinical impression of atrial septal defect by providing measurements of arterial saturations and pressures in cardiac chambers. Subsequently, the development of angiocardiography permitted direct visualization of abnormal communications between the atria and the anatomic features of such communications. In the late 1970s noninvasive visualization of atrial septal defects became possible with the development and application of two-dimensional echocardiography.

Surgical repair of atrial septal defects began in 1948. Initial techniques were dependent on suturing the defects using a rubber well sewn into an atrial opening. In this situation, the defect being repaired was not directly visualized.[13] Another early method used in repair of atrial septal defects was inflow occlusion, which was sometimes employed with hypothermia. Gibbon first employed cardiopulmonary bypass to close an atrial septal defect.[14] The technique of cardiopulmonary bypass greatly facilitated cardiac surgery, since it increased the time available for operative repair of defects and made it possible to operate with a bloodless field. Surgical procedures were soon developed for repair of all types of atrial septal and atrioventricular canal defects. In 1976, Mills and King[15] reported successful closure of an atrial septal defect by means of an occlusion device inserted by a catheter passed into the atrium. A modified catheter occlusion device for atrial septal defects designed by Rashkind and Cuaso is currently undergoing clinical trials.[16]

DEFINITIONS AND CLASSIFICATIONS

The anomalies considered in this chapter are all characterized by a direct opening between the left and right atria. Interatrial communications are considered in two groups: those resulting from abnormal development of the septa that normally partition the atrial portion of the heart into right and left atria and interatrial communications that result primarily from maldevelopment of partitioning of the atrioventricular canal and endocardial cushion defect anomalies (Fig. 60–1). The first group may be viewed as isolated atrial septal defects and the second group as atrioventricular canal defects.

Based on these considerations, the following classification scheme is used in this discussion:

Isolated atrial septal defects
- Probe-patent, valve-competent patent foramen ovale
- Atrial septal defect at the fossa ovalis (secundum atrial septal defect)
- Defect superior to fossa ovalis (sinus-venosus-type atrial septal defect, superior vena caval defect)
- Defect posterior and inferior to fossa ovalis (coronary sinus, inferior vena-caval-type atrial septal defect)
- Single atrium (common atrium)

Atrioventricular canal defects
- Complete forms
  - Divided anterior common leaflet
  - Divided anterior common leaflet without septal attachments
  - Undivided anterior common leaflet
- Incomplete forms
  - No interventricular communication
    - Partial forms
    - Intermediate forms
    - Transitional forms
    - With common atrium
    - Ostium primum atrial septal defect
    - Isolated cleft mitral valve
    - Isolated cleft tricuspid valve
  - With interventricular communication
    - Ventricular septal defect of atrioventricular canal type with normal atrioventricular valves
    - Ventricular septal defect of atrioventricular canal type with abnormal atrioventricular valves

The discussions that follow are separated into the two major subgroups of isolated atrial septal defects and atrioventricular canal defects.

ISOLATED ATRIAL SEPTAL DEFECTS

Embryologic Considerations

The atrial (receiving) partitioning of the primitive heart into the two atria of the fully developed heart results from the development of two septa known as septum primum and septum secundum. The names of these septa reflect the relative time of appearance of each in the embryo.[17,18] The septum primum develops during the fourth week of embryonic life as a more or less sickle-shaped sagittal fold in the middle of the primitive atrium that grows toward the endocardial cushions of the atrioventricular canal from the superior (cephalic) aspect of the primitive atrium. The concavity of the septum primum is directed inferiorly (apexward) toward the endocardial cushions of the atrioventricular canal. The opening at the inferior margin of the septum primum, which lies between it and the endocardial cushions of the atrioventricular canal, is the ostium primum. The ostium primum is most completely identified as the ostium primum of the septum primum. Prior to complete fusion of the septum primum with the endocardial cushions of the atrioventricular canal and closure of the ostium primum, a second opening appears in the septum primum. This second opening,

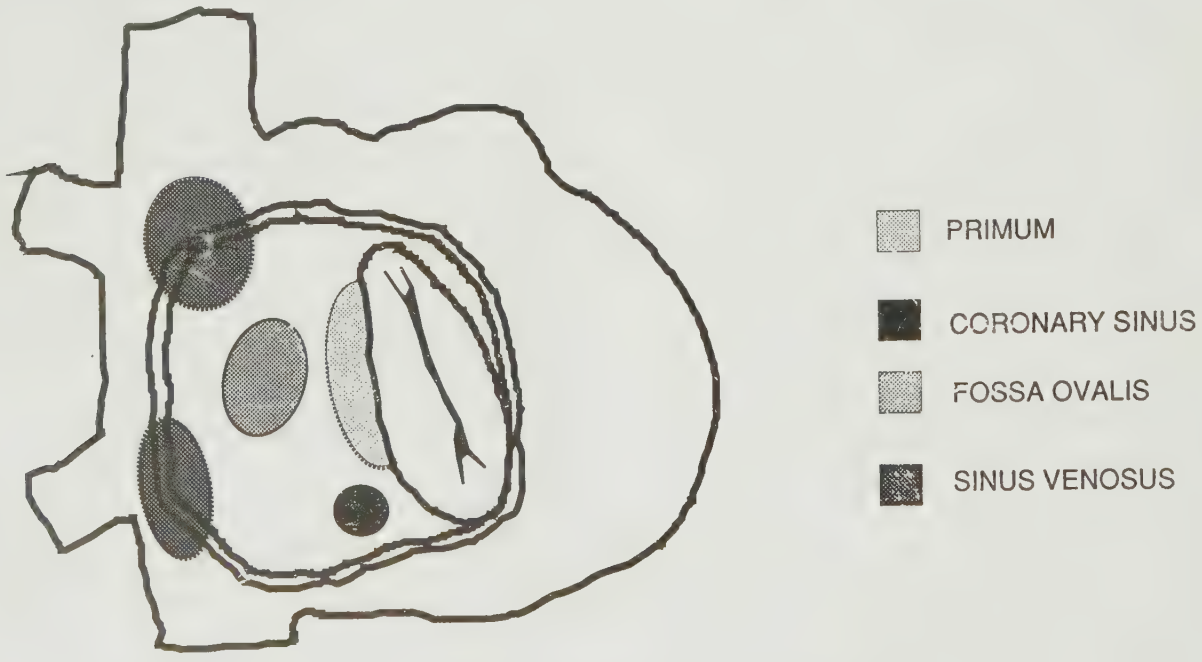

Fig. 60–1. Schematic diagram of the different types of atrial septal defect as viewed from the opened right atrium.

known as the ostium secundum, results from resorption of tissue in the superior part of the septum primum. The ostium secundum is more completely termed the ostium secundum of the septum primum.

The development of the ostium secundum of the septum primum occurs during the fifth and sixth weeks of embryologic life. At about the same time as the development of the ostium secundum, a second septum begins to develop. This septum is positioned to the right of the septum primum in the primitive heart and is known as the septum secundum. The septum secundum also is concave in shape, with the concavity directed more posteriorly toward the opening of the sinus venosus of the primitive heart. Its concave shape and its alignment permit the identification of two limbs of the septum secundum. One limb is located superiorly and the other is located inferiorly. The more inferior limb of the septum secundum fuses with the lowermost portion of the atrial septum, where it joins the endocardial cushion partitioning the atrioventricular canal.

The opening in the septum secundum resulting from its concave shape is termed the foramen ovale. The septum primum and septum secundum will fuse so that the foramen ovale of the septum secundum lies immediately to the right of the septum primum. As a result of the opening in the septum secundum (foramen ovale) and the opening in the septum primum (the ostium secundum), communication between the now separated right and left atria is possible, but only from right to left. Thus blood flow from the right atrium to the left atrium can and does occur through the foramen ovale of the septum secundum and the ostium secundum of the septum primum because the pulmonary vascular resistance of the developing lung exceeds the systemic vascular resistance and results in higher pressures in the right atrium of the fetus than in the left atrium. Atrial septal defects in this region may result from defective development of the septum secundum or from defective development (e.g., excessive resorption) of the septum primum. Accordingly, the true atrial septal defects in this region are best termed defects at the fossa ovalis, although by long-term usage, they are commonly referred to as secundum atrial septal defects. It should be noted that use of the term secundum to refer to these defects is correct only without any modifying adjectives such as ostium.

After birth, fusion of the two septa is completed in the region of the foramen ovale of the septum secundum and the septum primum, completely closing the ostium secundum of the septum primum and the foramen ovale. However, in approximately 25 to 30% of normal adult hearts, the flap of the septum primum does not completely fuse with the septum secundum. The septum primum then serves as a valve of the foramen ovale, which potentially could open and permit shunting when right atrial pressure exceeds left atrial pressure. Since in the normal postnatal state left atrial pressure exceeds right atrial pressure, the valve of the foramen ovale is usually closed.

Sinus venosus atrial defects lie outside the margins of the fossa ovalis. These defects are thought to be secondary to abnormal attachment of the right pulmonary veins to either the superior or inferior vena caval veins. An interatrial communication results when the wall between the vena caval and pulmonary veins is resorbed. Coronary sinus defects are thought to arise from failure of the wall between the coronary sinus and the left atrium to develop, so-called unroofing. Unroofing of the coronary sinus is frequently seen in the presence of a superior vena cava.

Epidemiologic Aspects

Fossa ovalis atrial septal defect is one of the most common congenital cardiac disorders. The study of Feldt et al.[19] in Olmsted County, Minnesota, showed that isolated secundum atrial septal defects accounted for approximately 7% of congenital cardiac defects. Most patients with isolated secundum atrial septal defects are females, by a factor of 2 to 1.

Genetic Aspects

Although fossa ovalis atrial septal defects usually occur sporadically, they may occur on a familial basis. The Holt–Oram syndrome is perhaps the best-known example of familial inheritance of atrial septal defects.[20] This disorder is characterized by congenital deformities of the upper limbs (most frequently absent or hypoplastic radii), electrocardiographic abnormalities such as right bundle block or first-degree atrioventricular block, and an autosomal dominant pattern of inheritance. There is a penetrance of nearly 100% with this disorder. Approximately 40% of the cases represent new mutations and the remainder are inherited from a parent. Although the Holt–Oram syndrome is apparently due to a single gene defect, the biochemical abnormality has not been defined at present.

Another example of familial inheritance of fossa ovalis atrial septal defects is the syndrome of familial atrial septal defect with prolonged atrioventricular conduction.[21] This mutant gene also has a high degree of penetrance but does not cause skeletal abnormalities. The identifying anomalies are prolonged atrioventricular conduction and the atrial septal defect in association with an autosomal dominant mode of inheritance.

In counseling patients and their parents, it is important to identify these syndromes, since 50% of first-degree relatives will be affected by them. By contrast, only 3% of first-degree relatives are affected with the usual sporadic type of atrial septal defect.

Anatomic Features

Valve-Competent Patent Foramen Ovale

Approximately 30% of otherwise normal adult hearts have a probe-patent, valve-competent foramen ovale, which is not usually considered an atrial septal defect.

Valve-Incompetent Patent Foramen Ovale

The smallest atrial septal defects are due to incompetent foramina ovale. They may be congenital or may be acquired by stretching of the right or left atria in conditions in which those chambers are enlarged.

Defects of the Fossa Ovalis

The typical fossa ovalis or secundum defect is contained within the area bordered by the limbus of the fossa ovalis. The size of these defects varies greatly. In addition, the atrial septum may be fenestrated, so that multiple defects are possible. Secundum defects may be confluent with other defects of the interatrial septum, such as a sinus venosus defect. The junction of the inferior vena cava and the right atrium is located slightly to the left of the limbus. Thus blood flowing in from the inferior vena cava has a tendency

to shunt from right to left across the septum. The eustachian valve has a tendency to overhang the atrial septum. This tendency can be important surgically, for it is possible to mistake the rim of the eustachian valve for the lower edge of an atrial septal defect.

Defect Posterior and Inferior to the Fossa Ovalis

Defects may exist posterior and inferior to the fossa ovalis. Hypoplasia or anterior displacement of the posterior limbus often coexists with these defects, as well as anomalous pulmonary venous connection of the right lung.

Sinus Venosus Defect

These defects are located in the part of the atrial septum subjacent to the superior vena caval orifice.[22] The right upper and middle-lobe pulmonary veins generally attach to the low superior vena cava or superior vena cava–right atrium junction in these patients, so that partial anomalous pulmonary venous return is present. Usually the superior vena cava overrides the atrium, so that some of the superior vena caval flow is directed into the left atrium, giving a right-to-left shunt. Occasionally, this override can be severe or even complete, with resultant marked cyanosis.

Coronary Sinus Defect

Coronary sinus atrial septal defects are characterized by absence of part or all of the common wall between the coronary sinus and the left atrium. A persistent left superior vena cava is also present in many cases.[23]

Associated Cardiovascular Defects

Atrial septal defects are often seen in conjunction with other congenital cardiac anomalies. In many of these anomalies, the associated defects are the lesions of primary importance. However, the atrial septal defect may still have a major role in the physiology of the lesion. A case in point is complete transposition of the great arteries, where an atrial septal defect allows the mixing between the pulmonary and systemic circulations necessary to sustain life. Another example is tricuspid atresia, in which the entire cardiac output must pass across the atrial septal defect.

Atrial septal defects are also frequently seen in conjunction with partial or total anomalous pulmonary venous connection. In total anomalous pulmonary venous connection the atrial septal defect is an essential feature, since the atrial septal defect is the only route whereby the pulmonary venous blood can return to the systemic circulation. Restriction of the atrial septal defect in affected individuals, which does occur, usually causes severe symptoms. Atrial septal defects are usually present with partial anomalous pulmonary venous return.

Acquired Cardiovascular Pathology Associated with Secundum Atrial Septal Defects

When the atrial septal defect is hemodynamically important, other cardiovascular structures are secondarily affected. The right atrial and the right ventricular size and thickness are increased. The pulmonary arteries are enlarged, and pulmonary vascular disease is sometimes present. Mitral valve prolapse may occur, a feature that is thought to result from the leftward shift of the ventricular septum caused by right ventricular enlargement.[24]

Patients with fossa ovalis atrial septal defects may contract rheumatic fever and develop mitral stenosis. This combination is termed Lutembacher's syndrome.[25] Mitral and/or tricuspid insufficiency may also develop in patients with atrial septal defects.

Physiology

Intrauterine and Postnatal

Because pulmonary blood flow is minimal before birth, nearly all blood reaching the left atrium must pass across the foramen ovale. When the lungs expand after birth, pulmonary venous return substantially increases and the systemic vascular resistance increases. The result in the normal infant is that left atrial pressure rises above the right atrial pressure, causing functional closure of the foramen ovale. When an atrial septal defect is present, the intrauterine physiology is essentially unchanged. However, the hemodynamic changes after birth do not close the atrial septum. Hence left-to-right shunting will tend to take place in these patients. Right-to-left shunting may also occur, and sometimes causes patients with atrial septal defect to exhibit mild cyanosis in the neonatal period.

Patent Foramen Ovale

If the flap valve of the foramen ovale is competent, shunting cannot occur as long as left atrial pressure remains higher than right atrial pressure. However, even in normal subjects, the right atrial pressure may transiently rise above the left atrial pressure. When this happens, right-to-left interatrial shunting may occur if the valve is functional. It is possible for blood clots and other emboli to pass across the atrial septum under these circumstances. In patients with pulmonary vascular disease or pulmonary stenosis, right-to-left shunting across a patent foramen ovale may occur.[26]

Defects of Small Size

We define small atrial septal defects as those that are associated with a Qp/Qs of less than 2:1 in the absence of significant associated cardiovascular anomalies. The presence of a small atrial septal defect does not cause major changes in cardiac hemodynamics. However, emboli can gain access to the left side of the circulatory system whenever the right atrial pressure rises above the left atrial pressure.

Defects of Moderate and Large Size

We define moderate and large atrial septal defects as being associated with a Qp/Qs of $\geq$2:1 in the absence of significant associated cardiovascular anomalies. In the presence of an atrial septal defect, the direction of the atrial shunting is determined by the relative pressures in the right and left atria. These atrial pressures are in turn principally determined by the resistances to filling of the respective ventricles. The amount of the resultant shunting is usually not dependent on the size of the interatrial communication, but rather on the relative compliance of the right and left ventricles.

During development, the atrial pressures in the cardiac cycle vary, as do the compliances of the right and left ventricles.[3] Immediately after birth the left and right ventricles are similar in compliance. Hence shunting tends to be minimal during the neonatal period, even with large defects. As the pulmonary vascular resistance drops and the right ventricle begins to assume its characteristic thin-walled configuration, the resistance to filling of the right ventricle drops also. For this reason, the left-to-right shunt

across atrial septal defects generally increases with time. Additionally, with increasing age the left ventricular compliance tends to increase, further increasing the tendency for left-to-right shunting.

When atrial defects are of large size, mean and phasic pressures will be equal when recorded by standard catheter measurements. Levin et al.[27] measured simultaneous right and left atrial pressures in patients with atrial septal defects using specially designed matched catheter systems to determine instantaneous pressure differences. All patients had a Qp/Qs of greater than 2:1. Shunt timing was determined by cineangiography, and the cine frames were related to the electrocardiogram with a photocell timing device. Though left atrial pressure was usually slightly higher than right atrial pressure during most of the cardiac cycle, the reverse was noted to occur transiently.[27] Thus a small right-to-left shunt of blood, predominantly from the inferior vena cava, occurred during early ventricular diastole or during the onset of ventricular contraction. Left-to-right pressure differences were most prominent during the second half of ventricular systole, with the peak differential occurring at the time of the left atrial *v* wave. The maximum left-to-right shunt was found to coincide in timing with this maximum pressure differential, after allowing for a 50- to 75-msec lag period.

The magnitude and duration of left-to-right and right-to-left atrial shunting varies with the respiratory cycle. Left-to-right shunting across the atrial septum is increased with the increased intrathoracic pressure of expiration and is decreased with the decreased intrathoracic pressure of inspiration. Right-to-left shunting across the atrial septum is decreased with the increased intrathoracic pressure of expiration and is increased with the decreased intrathoracic pressure of inspiration. Right ventricular hypertrophy and pulmonary disease increase the portion of the cardiac cycle during which right-to-left shunting takes place and increases the magnitude of the right-to-left shunt. Severe cyanosis can occur from right-to-left shunting when resistance to right ventricular inflow is high, as in critical pulmonic stenosis. When right-to-left shunting does occur across a secundum atrial septal defect, the shunted blood is derived primarily from the inferior vena cava, as blood from the superior vena cava tends to be directed across the tricuspid valve because of the orientation of the cardiac structures.

Physiology in Association with Additional Cardiovascular Pathologic Features

Right Ventricular Outflow Obstruction. As has been noted, patients with right ventricular outflow obstruction may develop sizable right-to-left shunts through an atrial septal defect or even a patent foramen ovale.[28,29] Severe obstruction will cause enlargement of the right atrium and may cause consequent stretching of the foramen ovale.

Pulmonary Vascular Disease. When pulmonary hypertension is present, the left-to-right shunt across the atrial septal defect is small and may be predominantly right to left. In some patients with pulmonary hypertension the presence of an atrial septal defect may be protective and prevent the development of acute right ventricular hypertension.

Left Ventricular Outflow Obstruction. Patients with left ventricular outflow obstruction will have increased resistance to filling of the left ventricle as opposed to the right ventricle. Hence they will tend to have a greater left-to-right shunt across the atrial septal defect than patients without left ventricular outflow obstruction.

Obstruction to Left Ventricular Inflow. Atrial septal defects are occasionally associated with congenital obstruction to left ventricular inflow, such as cor triatriatum and congenital mitral stenosis.[30–32] Patients with Lutembacher's syndrome develop acquired obstruction to left ventricular inflow. The atrial septal defect in these patients tends to ameliorate the left atrial (and consequent pulmonary venous) hypertension caused by the left ventricular inflow obstruction. However, the left-to-right shunting across the atrial septal defect (and hence the right ventricular volume overload) is increased.

Natural History

The natural history of small atrial septal defects seems to be excellent without specific therapy. Because these defects are difficult to detect, their incidence is probably clinically underestimated.

Isolated secundum atrial septal defects of moderate and large size do not cause major symptoms in most cases during infancy and childhood,[33–36] although occasionally even infants may develop severe congestive heart failure. In the absence of unrelated problems, over 99% of patients with isolated secundum defects will live past the first year of life. Children and infants with these defects tend to be smaller than normal, but failure to thrive on the basis of the atrial septal defect alone is rare. Exercise intolerance may develop in some patients as early as the second decade of life. Other may remain asymptomatic for several more decades.

As has also been noted, left-to-right shunting tends to increase with age in many patients. Thus the incidence of congestive heart failure with attendant fluid retention, hepatomegaly, and elevated jugular venous pressure rises with the age of these patients. The large shunts present in many older patients cause stretching of the atria, which presumably predisposes them to atrial arrhythmias, such as atrial flutter, fibrillation, and tachycardia. These arrhythmias increase in incidence with age and are a major cause of morbidity and mortality.

Sealy and colleagues[37] studied 108 preoperative patients with atrial septal defects ranging in age from 3 to 63 years and found an increased incidence of atrial arrhythmias in patients with large left-to-right shunts. Patients with a Qp/Qs of 2:1 or less had an 11% incidence of atrial arrhythmias, and patients with a Qp/Qs of 3:1 or greater had a 38% incidence of atrial arrhythmias. The incidence of arrhythmia was less than 25% in patients less than 30 years of age and greater than 50% in patients over 30 years of age. There was no evidence of a correlation between the incidence of arrhythmias and pulmonary artery pressure. Paroxysmal atrial arrhythmias, such as atrial flutter, atrial fibrillation, and supraventricular tachycardia, which are particularly likely to cause symptoms, were found by Brandenburg and colleagues[38] in 14% (27 of 188) of patients over 44 years of age with isolated secundum atrial septal defect. Atrial fibrillation or atrial flutter was present preoperatively in 38% (6 of 16) patients over 60 years of age treated surgically by Brandenburg and colleagues.[38] By contrast, only 2% of 204 patients with atrial septal defect less than 18 years old studied by Boelkens and colleagues had atrial arrhythmias of any kind.[39]

Pulmonary vascular disease may develop in patients with atrial septal defect. This complication is infrequent in childhood and

adolescence and uncommon even in older adults with large defects. Steele and colleagues reviewed the histories of 702 patients with isolated secundum or sinus venosus atrial septal defects and identified 40 patients (6%) with pulmonary vascular obstructive disease.[40] Most (34 of 40) of these patients were females and all were over 19 years of age. It is of note that the proportion of females with pulmonary hypertension in this series substantially exceeds the 2:1 predominance of atrial septal defect in females. A high mortality rate was associated with a total pulmonary resistance of greater than 15 units/m^2, regardless of whether treatment was medical or surgical. Surgical treatment improved outcome in patients with a total pulmonary resistance of less than 15 units/m^2. Seventeen of the 40 patients died during the followup period, which had a median length of 12 years. Two patients died within 24 hours after technically successful surgery and two patients died from noncardiac causes. Cardiac failure was cited as the cause of death in all other deaths.[40]

The childhood incidence of pulmonary vascular disease in association with atrial septal defect may be relatively high in certain regions, however. Cherian and colleagues reported an incidence of pulmonary vascular disease of 7% in the first decade of life and 8% in the second decade of life in a series of 709 patients with isolated secundum atrial septal defect from Vellore, India.[41] Dalen and associates[42] found that pulmonary hypertension was more common in patients less than 20 years of age with atrial septal defect who lived at an altitude in excess of 4000 ft than in such patients who lived at an altitude of 2000 ft or less. Pulmonary hypertension was present in 11 of 53 patients living at an altitude of 4000 ft or more as opposed to 3 of 49 who resided at an altitude of 2000 ft or less.

The incidence of elevated pulmonary vascular resistance in patients with atrial septal defect increases with increasing age, and serial studies in some patients have demonstrated progression of disease with time, presumably due to continued damage to the pulmonary vasculature by elevated pulmonary blood flow. However, the rate of this progression is highly variable. Furthermore, it has been well documented that patients with large atrial septal defects and high pulmonary blood flow may survive until the sixth or seventh decade of life without developing elevated pulmonary artery pressure or resistance. Conversely, advanced pulmonary vascular disease has been reported in patients with atrial septal defect as young as 2 years of age.[43] This information suggests that factors other than elevated pulmonary blood flow are important causes of pulmonary vascular disease in these patients. Rabinovich and colleagues have suggested that a biologically deficient form of von Willebrand factor may contribute to the development of pulmonary vascular disease in patients with congenital heart disease, including atrial septal defect.[44]

Bacterial endocarditis is rare in patients with atrial septal defect in the absence of associated anomalies, and antibiotic prophylaxis is not uniformly recommended.[45,46] Paradoxical emboli may occur, however, even with small defects. The presence of an atrial septal defect should be considered in any patient with a cerebral or other systemic embolus in which there is no demonstrable left-sided source, particularly if there is systemic venous thrombosis.[47] Patients in whom fibrillation develops often have atrial thrombi, which may embolize systemically.

It has become apparent that a substantial number of atrial septal defects detected during infancy will close spontaneously. Kavey and colleagues[48] identified patients with secundum atrial septal defects using two-dimensional echocardiography in conjunction with physical examination, electrocardiography, and chest roentgenograms. After a followup period of at least 2 years, 17 of the patients no longer had echocardiographic or other findings consistent with atrial septal defect by a mean age of 4 years. Spontaneous closure of atrial septal defect has also been documented by cardiac catheterization. Cockerham and colleagues[49] detected the presence of an isolated secundum atrial septal defect by cardiac catheterization and cineangiography in 54 patients less than 2 years of age. None of the patients had obstructive lesions of the left side of the heart. It was documented at a subsequent catheterization that the atrial septal defect in 14 of these patients had completely closed. Other investigators have also described complete closure of atrial septal defects in early childhood.[50]

Atrial Septal Defect and Pregnancy

Pregnancy is generally well tolerated in patients with atrial septal defect who do not have pulmonary vascular disease. Espino Vela and Alvarado-Toro described a series of 105 patients with isolated atrial septal defect in which there were no deaths.[51] Pregnancy does place additional demands on the cardiovascular system, and may cause patients with previously occult atrial septal defects to become symptomatic. In particular, exercise intolerance and congestive heart failure may become apparent during pregnancy. Venous thrombosis, common during pregnancy because of stasis, may lead to paradoxical embolism when an atrial septal defect is present.[52,53] Pulmonary vascular disease is rare below the age of 30 in patients with atrial septal defect in most ethnic groups and geographical regions, but when it is present, pregnancy carries a substantial health risk for the mother and often results in miscarriage.[54,55] In these patients, maternal mortality may approach 50%. Causes of maternal death include preeclampsia, hemorrhage, and thromboembolism.[56]

Physical Examination

Inspection and Palpation

The height and weight of patients with atrial septal defects is often below normal, though usually not by substantial margins. A precordial bulge may be present in those with a large left-to-right shunt, and Harrison's grooves (transverse depressions on both sides above the lower border of the thorax) may be apparent in some patients.[29] The presence of a hypoplastic thumb or radius, or phocomelia should cause suspicion that the patient has the Holt–Oram syndrome.[20] Cyanosis may be present in infants, particularly those with right ventricular outflow obstruction. Cyanosis may also be present in the relatively unusual patient with pulmonary vascular disease. On occasion a large eustachian valve may direct inferior vena caval flow across a secundum defect or a sinus venosus defect of the inferior vena caval type.

In patients with a thin body habitus, a hyperdynamic right ventricular impulse may be observed. Palpation along the left sternal border and in the subxiphoid area will demonstrate this impulse,[57] often termed a right ventricular heave. When pulmonary vascular disease is present, or when obstruction to right ventricular outflow is present, the right ventricular impulse will be less dynamic and will have more of a tapping or thrusting quality, concomitant with the change from pressure to volume overload. An enlarged and

pulsatile pulmonary trunk may also be palpated in many patients at the second left intercostal space. When pulmonary hypertension is present, the impulse created by the pulmonary artery is even more prominent. A palpable pulmonic component of the second heart sound may be present in such patients.

Arterial Pulse. The arterial pulse is normal at rest in these patients. It is possible to demonstrate abnormalities when the Valsalva maneuver is employed, however.[58] During the straining phase of the Valsalva maneuver, normal subjects show a decrease in systemic venous return. In patients with atrial septal defects and relatively large left-to-right shunts, the large volume of blood pooled in the lungs permits left ventricular output to be maintained.

Jugular Venous Pulse. Patients with isolated and nonrestrictive atrial septal defects have a jugular venous pulse of normal amplitude. However, since the two atria are connected by a nonrestrictive channel, the A and V waves have equal height.[59] When pulmonary vascular disease supervenes, the right atrium contracts more forcefully, causing large A waves to be formed.[29]

Auscultation

The first heart sound, best heard at the apex and lower left sternal edge, is often split with atrial septal defects, and the second component is increased in intensity. This increased intensity is thought to result because the high amount of diastolic flow presses the leaflets toward the right ventricle and because the forceful right ventricular contraction causes an abrupt cephalad excursion of the tricuspid leaflets.

Atrial septal defects with moderate to large left-to-right shunts are associated with a pulmonary systolic murmur which begins shortly after the first heart sound, peaks in early to midsystole, and ends before the second heart sound. This murmur is not usually associated with a thrill. When a thrill is present, either a very large shunt or a pulmonic stenosis is frequently present. Rapid flow through the peripheral pulmonary arteries may cause systolic crescendo–decrescendo murmurs, which are most prominent at locations in the chest other than the second intercostal space.

The characteristic auscultatory finding in atrial septal defect is wide, fixed splitting of the second sound.[60,61] This finding is present in patients with large left-to-right shunts and normal pulmonary artery pressure. Two principal theories have been developed to explain fixed splitting of the second sound in atrial septal defect.[61,62]

The first explanation relates splitting of the second sound to the variations in systemic and pulmonary venous return created by inspiration and expiration, and the consequent effect on flow across the atrial septal defect.[61] In normal subjects the decreased intrathoracic pressure of inspiration augments systemic venous return and thus increases right ventricular stroke volume and ejection time. Concomitantly, pulmonary venous return to the left side of the heart is decreased, and left ventricular stroke volume and ejection time are decreased. Thus splitting of the second sound increases with inspiration in normal subjects. Expiration is associated with reduced systemic venous return, decreased right ventricular stroke volume, and decreased right ventricular ejection time. There is also increased pulmonary venous return with expiration, resulting in an increase in left ventricular stroke volume and ejection time. Therefore splitting of the second sound decreases with expiration in normal subjects.

In patients with atrial septal defect, the flow across the defect is diminished by the reduced pulmonary venous return of inspiration and increased by the increased pulmonary venous return of expiration. Since inspiration increases and expiration decreases systemic venous return, it follows that flow across the defect and systemic venous return change in a reciprocal manner, so that ventricular stroke volumes and ejection times remain essentially constant. As a consequence, the time difference between aortic and pulmonary valve closure is unchanged with respiration.

The second theory is based on evidence suggesting that pulmonary capacitance is the major factor in determining splitting of the second sound.[62] According to this explanation, inspiratory splitting of the second sound in normal subjects results primarily because pulmonary capacitance increases during inspiration. This increase in capacitance causes an inspiratory increase in the "hangout" interval (the time between the descending portions of the right ventricular and pulmonary arterial pressure pulses) and a consequent delay in the pulmonic component of the second sound. In normal subjects the pulmonary capacitance decreases upon expiration, there is a decrease in the hangout interval, and the splitting of the second sound decreases.[63]

In patients with atrial septal defect the capacitance of the pulmonary bed is increased and its impedance is decreased.[62] The increased capacitance causes an increase in the hangout interval and a consequent wide splitting between the first and second sounds. There is little respiratory variation in the pulmonary capacitance and consequently little variation in the hangout interval and splitting of the second sound.

The duration of electromechanical systole is the same in the right and left ventricles of these patients, because even though the right ventricle ejects a relatively larger volume than the left ventricle, it ejects it in an accelerated manner. If the pulmonary arterial pressure rises, the hangout interval decreases, but the split still does not vary with the phase of the respiratory cycle.

When the left-to-right shunt is small or negligible, as it is in most neonates with atrial septal defects, fixed splitting of the second sound does not occur. Fixed splitting does not occur in patients with partial anomalous pulmonary venous return and intact atrial septum, presumably due to the lack of reciprocal changes in left-to-right shunt and systemic venous return with inspiration.[64] Since relatively wide (but not truly fixed) splitting of the second sound is common in the supine position, it is better to evaluate the second sound when the patient is sitting or standing.

The intensities of the pulmonic and aortic components of the second sound are equal in most patients with uncomplicated atrial septal defects, probably because the main pulmonary artery is dilated and close to the chest wall. By contrast, in normal subjects the aortic component of the second sound is louder than the pulmonic component.[65] Patients with pulmonary hypertension generally have an accentuated pulmonic component of the second sound. However, occasionally a patient with normal pulmonary arterial pressures will have an increased intensity of the pulmonic component of the second sound.

The diastolic murmur most commonly associated with atrial septal defect is a mid-diastolic murmur associated with the high flow across the tricuspid valve. This murmur becomes apparent when the left-to-right shunt across the atrial septal defect is greater than 2 to 1. The murmur is of low to medium frequency and does not increase with inspiration. Another diastolic murmur sometimes associated with atrial septal defect is a low-pitched murmur of

pulmonic regurgitation, which is thought to be a consequence of dilatation of the pulmonary artery.

Because the pressure gradient across the atrial septum is seldom large, audible murmurs from flow across the atrial septal defect itself are rare, though intracardiac phonocardiography can demonstrate them.

In the occasional patient with atrial septal defect and right-to-left shunting due to pulmonary hypertension, auscultatory findings differ greatly from those usually found in atrial septal defects.[66] A right ventricular fourth heart sound may be present. The midsystolic pulmonic murmur is softer and shorter since only a normal stroke volume is ejected. The tricuspid flow murmur is not present. The pulmonic component of the second sound is increased in intensity but the fixed splitting narrows. If a murmur of pulmonic insufficiency is present, it is high-pitched. A holosystolic murmur of tricuspid insufficiency may also be present.

The auscultatory findings in mild valvular pulmonic stenosis or infundibular stenosis and idiopathic dilatation of the pulmonary artery may mimic those of atrial septal defect. All these disorders are associated with a systolic murmur and a split second sound. They may be differentiated from atrial septal defects by movement of the second sound with respiration, by a pulmonary ejection click, or by the absence of a tricuspid flow murmur. As has been noted, in atrial septal defect, the second sound does not move with respiration, and a tricuspid flow murmur is frequent. Pulmonary ejection clicks are uncommon in atrial septal defects uncomplicated by pulmonary hypertension.

Electrocardiogram

Sinus rhythm is usual in young patients with uncomplicated secundum atrial septal defects. However, electrophysiologic studies have demonstrated a substantial age-related incidence of sinus-node dysfunction beginning in early childhood.[67–69] Ruschhaupt and colleagues[68] evaluated 34 patients with secundum atrial septal defects prior to surgical intervention and found that 13 (38%) had a delayed sinus-node recovery time as a result of right atrial pacing. Sinus-node recovery times were prolonged in 7 of 10 patients older than 5 years of age, in 6 of 11 patients between 2.5 and 5 years of age, and in none of the 13 patients less than 2.5 years old. Clark and Kugler[67] found electrophysiologic evidence of sinus-node dysfunction before operation in 10 of 15 patients with atrial septal defects. Their patients had a mean age of 8 years and 5 were younger than 5 years of age.

Atrioventricular node dysfunction is less common than sinus-node dysfunction in patients with secundum atrial septal defect, but is not unusual.[69] Prolongation of the P–R interval is frequent and sometimes has a familial association. Beyond the third decade of life, patients with atrial septal defect have a high incidence of atrial arrhythmias, particularly atrial fibrillation, but also including atrial flutter and supraventricular tachycardia.[70]

Patients with atrial septal defects usually have a normal P wave. Occasionally, a particularly broad P wave is present that is not notched or bifid. This effect is thought to be caused by an enlarged right atrium. P waves seen in patients with secundum atrial septal defect may be peaked, but they are seldom of high amplitude. In secundum atrial septal defects, the frontal-plane P-wave axis is normally directed to the left and downward.

Sinus venosus atrial septal defects are often associated with a leftward frontal plane P-wave axis, negative in III and aVF and positive in aVL. Davia and colleagues found a frontal-plane P-wave axis of 0° or less in 13 of 48 patients.[22] Similar findings were present in the preoperative electrocardiograms reviewed by Kyger and colleagues.[71] When a persistent left superior vena cava is also present, a leftward frontal axis seems to be particularly common. Two explanations have been offered to account for the abnormal P-wave axis in patients with sinus venosus atrial septal defect. First, it has been suggested that the sinoatrial node in patients with sinus venosus atrial septal defects is displaced to a relatively inferior location, causing a shift in the pattern of atrial activation.[22] The second explanation, applicable in those cases with persistent left superior vena cava, is that an ectopic atrial pacemaker is present, a persistent remnant of the embryonic pacemaker present at the junction of the left common cardinal vein with the sinus venosus.[72] The first explanation does not account for the presence of a normal P-wave axis in most cases of sinus venosus atrial septal defect, and the second explanation does not account for the relatively frequent presence of a leftward frontal-plane P-wave axis in patients with no persistent left superior vena cava.[22] Thus neither explanation is entirely satisfactory. Unfortunately, the available morphologic information regarding the sinus node in sinus venosus atrial septal defect is limited.[73]

The QRS complex in patients with secundum atrial septal defects often has a slightly prolonged duration and a characteristic rSr′ or rsR′ pattern[74] (Fig. 60–2). The terminal r′ or R′ is often moderately slurred. Thus the terminal forces of the QRS complex are directed to the right, superiorly and anteriorly. The reason for this orientation of the QRS complex is thought to be disproportionate thickening of the right ventricular outflow tract, which is the last portion of the ventricle to depolarize. The term ''incomplete right bundle branch block'' is often used to describe this QRS pattern, but is a misnomer, since it is a consequence of hypertrophy, and not a conduction disturbance.

With increasing degrees of pulmonary hypertension, patients with secundum atrial septal defects tend to lose the rSr′ pattern in lead V_1 and develop a tall monophasic R wave with a deeply inverted T wave.

A frontal-plane QRS axis ranging from +95° to +135° with a clockwise loop is often present. Left-axis deviation of the QRS axis with a counterclockwise frontal-plane loop suggests the presence of an atrioventricular canal defect, but can occur with uncomplicated secundum atrial septal defect.

Chest Roentgenogram

The chest roentgenogram in patients with secundum atrial septal defect and sizable left-to-right shunts generally shows cardiac enlargement and increased pulmonary vascularity[75] (Fig. 60–3). The increased pulmonary vascularity typically extends to the periphery of the lung fields, with a dilated pulmonary trunk and central branches. Although the ascending and transverse aortas have normal diameters in these patients, the enlargement of the pulmonary arteries causes the aorta not to form the border of the cardiac silhouette. The consequence is that a characteristic ''triangular'' cardiac shape is created. Right atrial and right ventricular enlargement are usually seen, but left atrial and left ventricular sizes are usually normal.

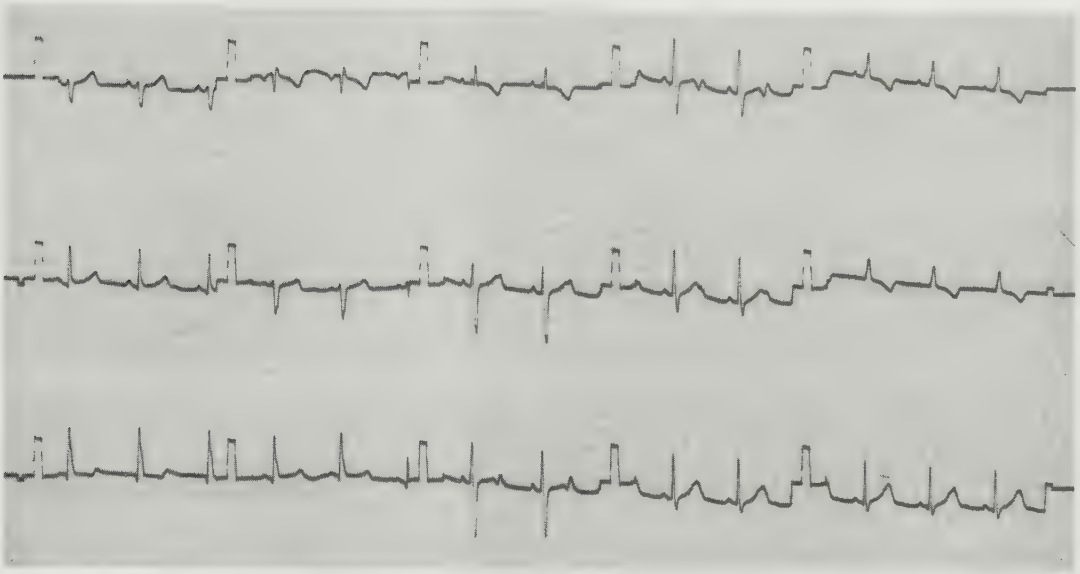

Fig. 60–2. Electrocardiogram from a 9-yr-old girl with a large secundum atrial septal defect. Note the rsR′ in lead V_1 and the rightward deviation of the frontal-plane QRS axis.

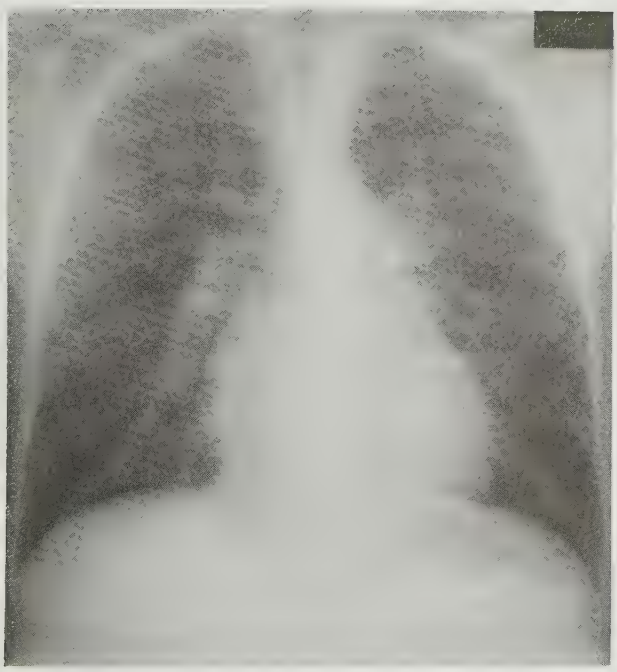

Fig. 60–3. Chest roentgenogram from a 9-yr-old girl with a secundum atrial septal defect and a large left-to-right shunt (electrocardiogram shown in Figure 60–2). The pulmonary artery vasculature is increased. The main pulmonary artery is enlarged. The ascending aorta is relatively inconspicuous.

Echocardiogram

M-Mode

The M-mode echocardiogram in patients with classic secundum atrial septal defect will usually show right ventricular enlargement, and paradoxical motion of the interventricular septum will be present in many cases.[76,77] Mitral valve motion appears normal in these patients, as opposed to those with atrioventricular canal defects, in whom the M-mode echocardiogram shows apparent diastolic motion of the mitral valve through the interventricular septum.

Two-Dimensional

Two-dimensional echocardiography can provide direct noninvasive visualization of all types of atrial septal defects[78–80] (Fig. 60–4). The reliability of the two-dimensional echocardiogram in demonstrating characteristic dropout in the atrial septum is best when the axis of the echo beam is perpendicular to the atrial septum. For most defects, a subcostal view provides such a perpendicular angle, though, depending on the location of the defect, there are other possible echocardiographic approaches, such as suprasternal or parasternal, that will yield an appropriate angle. Atrial septal defects can often be seen on the apical four-chamber view, but as a consequence of the parallel angle of the echo beam to the atrial septum and the thinness of the fossa ovalis, false echo dropout is often seen.

In addition to direct visualization of the atrial septal defect, two-dimensional echocardiography will also frequently demonstrate enlargement of the right atrium, right ventricle, and pulmonary arteries and will often show the paradoxical motion of the interventricular septum in a two-dimensional format. In many cases the pulmonary venous connections can be demonstrated.

Doppler

Abnormal flow across the atrial septum can be reliably detected by pulsed Doppler echocardiography.[81] The accuracy of Doppler

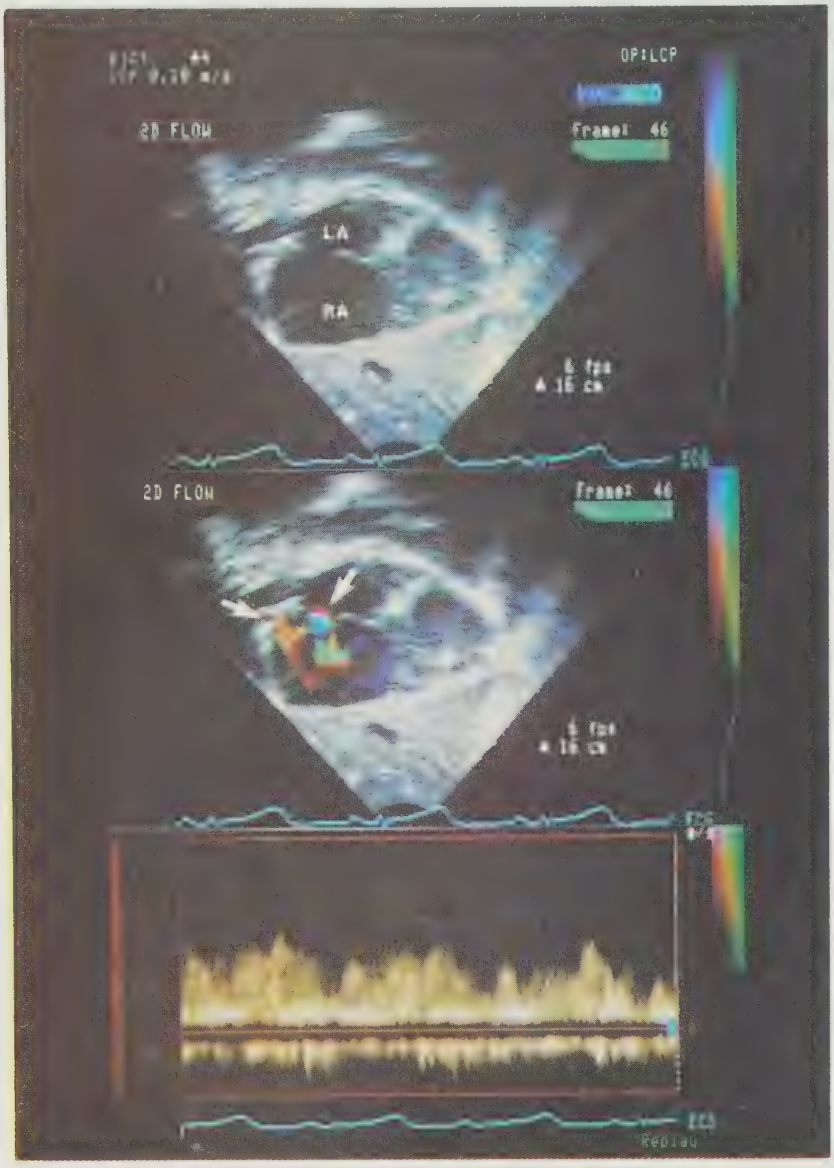

Fig. 60–4. Upper panel—Two-dimensional echocardiogram (subcostal view, anatomical orientation) demonstrating a secundum atrial septal defect between the left atrium (LA) and right atrium (RA). Middle panel—Color Doppler study of atrial flow in the same patient. Arrow on the patient's left indicates flow into the atrium from the superior vena cava. Arrow on the patient's right indicates left-to-right flow across the secundum atrial septal defect into the right atrium. Lower panel—Pulsed Doppler study with sample volume positioned over atrial septal defect demonstrates presence of flow toward the transducer, consistent with the presence of left-to-right shunting.

identification of flow across the atrial septum can be greatly improved by the use of two-dimensional echocardiographic direction of the Doppler sampling. Characteristically, a shunt across the atrial septal defect will show turbulent flow in the direction of the shunt and minimal flow in the opposite direction. With classic secundum atrial septal defects, the interatrial shunt occurs in late systole and early diastole. Since pressure gradients across the atrial septum are characteristically minimal when the defects are nonrestrictive, velocity is usually low.

Pulsed Doppler echocardiography can aid in the quantitation of pulmonary-to-systemic blood flow. By integrating the time-velocity Doppler tracings taken at either the tricuspid and mitral orifices or the pulmonic and aortic orifices and multiplying by the respective valve areas measured by two-dimensional echocardiography and by the heart rate, estimates of the right and left ventricular outputs and Qp/Qs can be obtained that agree relatively well with catheterization data.

Continuous-wave Doppler echocardiography can be of assistance in the assessment of patients with atrial septal defect. It is particularly useful in estimating the pressure gradient across the atrial septum in patients with left atrial hypertension and restrictive atrial septal defects, and in evaluating patients for obstruction to pulmonary venous return.[82]

Color Doppler also provides useful diagnostic information in these patients.[83,84] It allows for the direct visualization of the flow across the atrial defect and is particularly helpful in distinguishing normal right superior vena caval flow from abnormal left-to-right shunting across the atrial septum.

If additional confirmation of diagnosis is desired, contrast echocardiography using agitated saline or indocyanine green is effective in demonstrating the presence of atrial septal defects. A right-to-left shunt can be detected by direct visualization of microcavitation bubbles in the left atrium and left ventricle. A left-to-right shunt can be detected as a negative contrast washout effect in the right atrium provided good opacification of the atrium is achieved.[85] The presence of an unroofed coronary sinus in conjunction with

a persistent left superior vena cava can be demonstrated echocardiographically by injection of agitated saline or idocyanine green into a left arm vein. When the coronary sinus is unroofed, and a left-to-right shunt is present, echocontrast will be seen to opacify the left atrium prior to opacifying the right atrium.

Radionuclide Angiocardiography

After peripheral venous injection of radionuclide, the time–activity curve of radioactivity measured over the lungs will show a characteristic pattern due to recirculation in patients with intracardiac left-to-right shunts. Analysis of these curves with any of several methods will provide an estimate of the Qp/Qs ratio that under optimal conditions correlates well with catheterization results. This method has reduced accuracy in the presence of tricuspid or pulmonary regurgitation and is dependent on the injection of a rapid, discrete bolus of radionuclide. In selected patients, measurement of right and left ventricular ejection fraction with either the first-pass technique or gated blood pool studies may be clinically useful.[86]

Nuclear Magnetic Resonance Imaging

With appropriate techniques, the atrial septum can be demonstrated by magnetic resonance imaging.[87] Because cardiac motion tends to degrade the images, studies should be synchronized with the cardiac cycle, usually with use of the electrocardiogram. Most investigators have used the spin echo technique because this method provides good contrast between the cardiac chambers and blood vessels and flowing blood. However, recently developed flow-sensitive methods have the capability of demonstrating cardiac blood flow in cine format and may also prove useful. Magnetic resonance is particularly helpful in the evaluation of the pulmonary venous connections in atrial septal defect.

Cardiac Catheterization

Cardiac catheterization may not be essential for management when the result of noninvasive tests clearly demonstrate the presence of an atrial septal defect without associated anomalies.[88] When pulmonary vascular disease is suspected, however, determination of pulmonary vascular resistance by catheterization is indicated.[5] Patients with a pulmonary vascular resistance of greater than 12 to 14 units · m^2 are generally considered inoperable. Cardiac catheterization and appropriate cineangiography can be helpful in the evaluation of anomalies associated with atrial septal defect, such as partially anomalous pulmonary venous return or mitral valve disease.

Secundum atrial septal defect can sometimes be differentiated from sinus venosus and atrioventricular canal defects because characteristic high and low catheter courses across the atrial septum are seen with the latter two defects, whereas in atrial septal defect, the catheter passes across the middle portion of the atrial septum.

Left-to-right shunting across the atrial septum causes an increase or "step-up," in oxygen saturation in the right atrium. An increase of 10% over superior vena caval blood in one oxygen saturation series or an increase of 5% in two series is generally indicative of the presence of a left-to-right shunt at the atrial level. Exceptional situations that give similar results in oxygen saturation data without interatrial communications are ventricular septal defect with tricuspid insufficiency, left ventricular to atrial communication, and partial anomalous pulmonary venous return without atrial septal defect. When mixed venous and systemic arterial blood samples are obtained, the standard Fick equation can be used to calculate the ratio of pulmonary to systemic blood flow, Qp/Qs. Indicator dilution injections can be employed for obtaining both qualitative and quantitative information about shunt flow. Right-to-left shunting can be demonstrated with this technique, the presence of anomalous pulmonary venous return can be inferred when it is present, and Qp/Qs can be quantitated. The presence of an unroofed coronary sinus with left-to-right shunting can be identified by continuous oximetry employing a fiberoptic catheter pulled back in the coronary sinus.[89]

Intracardiac pressures and pressures in the great vessels can be directly measured at cardiac catheterization. Pressure gradient across the atrial septal defect is minimal in most patients with secundum atrial septal defect and often is obscured when fluid-filled catheter systems are used. Catheter-tip pressure transducers give more accurate pressure tracings, though they are technically more difficult to operate. Many patients with atrial septal defect and large left-to-right shunts will have a substantial pressure gradient across the pulmonary valve. This gradient is usually related to the high blood flow across the pulmonary outflow tract and resolves after surgical closure of the atrial septal defect. Such flow-related gradients may be as high as 40 mm Hg.

Cineangiography

The presence of an atrial septal defect with left-to-right shunting can be demonstrated in the anteroposterior and lateral projections by an injection of contrast medium into the main pulmonary artery. Contrast material can be seen to pass into the right atrium and ventricle and may reflux into the hepatic veins after such an injection in patients with atrial septal defects. A pulmonary artery injection is also a good method for evaluation of the pulmonary venous return and will usually demonstrate any abnormal connections. Although this technique is useful for demonstrating the presence of atrial septal defect, it does not provide good visualization of the size and location of atrial septal defects. For optimal direct visualization, an injection just outside the orifice of the right upper pulmonary vein in the cranially angulated left anterior oblique projection (often termed the "four-chamber" view) is the most appropriate examination.[90] With the four-chamber view, secundum atrial septal defects will be demonstrated in the middle of the atrial septum, sinus venosus defects of the superior vena caval type will be demonstrated at the top, and atrioventricular canal defects will be shown at the bottom (Figs. 60–5 and 60–6). Angiographic definition of coronary sinus atrial septal defect is made by selective injection into the left superior vena cava, pulmonary vein, or left atrium (Fig. 60–7). In the absence of elevated right atrial pressure, contrast material is seen to pass into the left atrium, inferiorly to the coronary sinus, and then into the right atrium.[91]

Treatment

It is generally agreed that secundum atrial septal defects associated with a large left-to-right shunt and either symptoms or

Fig. 60–5. Frame from a cineangiogram taken in the hepatoclavicular projection after injection at the orifice of the right upper pulmonary vein in a patient with a large secundum atrial septal defect. Note the location of the defect in the center of the atrial septum.

significant cardiomegaly should be electively closed in childhood. When the findings of a comprehensive noninvasive evaluation demonstrate a classical secundum atrial septal defect with no evidence of elevation of pulmonary artery pressure, many physicians believe that cardiac catheterization is not essential. When the atrial shunt is small or pulmonary hypertension is present, recommendations regarding closure are more controversial.[92] Small defects generally cause minimal difficulty and have a good prognosis. Therefore the gain from closing them may not be worth the risk of cardiopulmonary bypass. When advanced pulmonary vascular

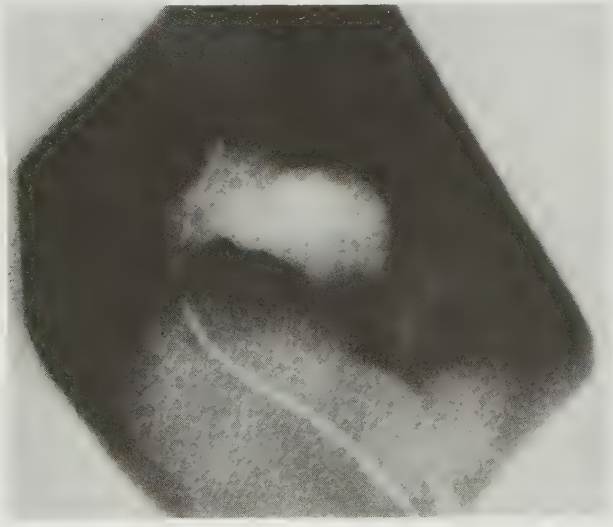

Fig. 60–6. Frame from a cineangiogram taken in the hepatoclavicular projection after injection at the orifice of the right upper pulmonary vein in a patient with a sinus venosus atrial septal defect. Note the contrast passing across the atrial septum at its uppermost portion.

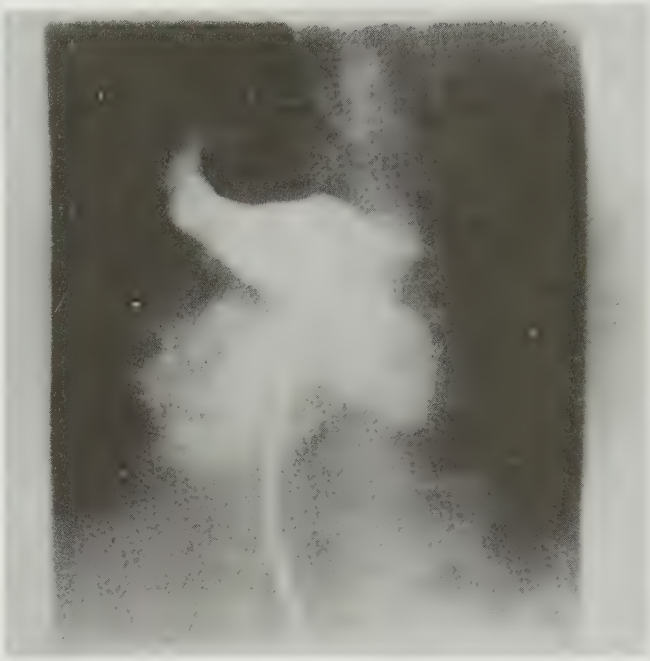

Fig. 60–7. Frame from a cineangiogram taken in the hepatoclavicular projection after injection at the orifice of the right upper pulmonary vein in a patient with a large coronary sinus atrial septal defect. Note the location of the defect at the lowermost portion of the atrial septum.

disease is present, operative mortality and morbidity are high and closure of the atrial septal defect may actually worsen the prognosis.[93]

Surgical closure is almost invariably performed with the aid of cardiopulmonary bypass. Successful closure can be accomplished by direct suture or with either pericardial or Dacron patches.[94,95] Closure of large defects by direct suture can distort the atrium. Successful catheter closure of secundum atrial septal defects with occlusion devices has been performed and the method shows promise, particularly for the closure of small defects in the fossa ovalis area.

Repair of sinus venosus atrial septal defects requires a patch to redirect the right pulmonary venous return into the left atrium.[96] The patch must be placed in such a manner that pathways of adequate size are provided for the superior vena caval and pulmonary venous flow, since obstruction can result if these pathways are inadequate. The location of the sinus node, which is usually lateral to the superior cavoatrial junction but occasionally is located at the top of the right atrial appendage, is well away from the interatrial communication in patients with sinus venosus atrial septal defect. However, the blood supply of the sinus node is variable, and could potentially be compromised by surgery in the region of the superior vena caval–atrial junction. The sinus-node artery arises from either the right coronary artery (55% of cases) or the left coronary artery (45%). Anderson et al.[97] determined that the sinus-node artery approached the node from a posterior aspect in 11 of 25 hearts and from an anterior aspect in 10. Dual sinus-node arteries were present in four cases, approaching the node from both anterior and posterior aspects.

Repair of coronary sinus atrial septal defects is complicated by

the close proximity of the atrial septal defect to the atrioventricular node. Sutures must be placed very close to the superior rim of the defect in order to avoid heart block. Therefore a patch is recommended for defect closure in these cases. Coronary sinus atrial septal defects are frequently associated with a persistent left superior vena cava.[98] If the persistent left superior vena cava can be occluded without elevation in jugular venous pressure, it can be ligated. However, if jugular venous pressure is elevated after occlusion of the persistent left superior vena cava, a pericardial baffle repair has been recommended.[99] With this technique, the atrial septum is partially excised and replaced with a pericardial baffle, which redirects the flow of the persistent left superior vena cava into the right atrium and closes the interatrial communication.

Regardless of the type of atrial septal defect to be closed, care should be taken with venous cannulation. The technique of venous cannulation through the right atrial appendage has been successful in many patients. However, there is potential for damage to the sinoatrial node if a clamp is placed too proximal on the appendage at the beginning or end of the cannulation. Therefore some investigators have suggested use of cannulation at sites far removed from the sinoatrial node.[94,100,101]

Prognosis

Surgical results in uncomplicated secundum atrial septal defect are good. Mortality is less than 2% in many large series.[102–104] Whether or not life expectancy becomes completely normal after surgical closure of an uncomplicated secundum atrial septal defect in childhood remains to be determined. Most children undergoing atrial septal defect closure are asymptomatic before operation. Cardiac enlargement on chest roentgenogram may resolve in these children, and electrocardiographic evidence of right ventricular hypertrophy may disappear. Young[105] reported that heart size on chest roentgenogram was initially enlarged and returned to normal in 65% (46 of 71) of children with secundum atrial septal defect within 2 years after repair. In 86% of his patients, there was a shift of the QRS axis to the left and a decrease in the height of the R or R′ wave in lead V_1 after surgery.

However, in a substantial fraction of children undergoing repair of atrial septal defect (19 of 71, or 27%, in Young's series), regression of heart size to normal on chest roentgenogram does not occur. Electrocardiographic evidence of right ventricular hypertrophy may also persist in some patients (3 of 71, or 4%, in Young's series). Furthermore, right ventricular enlargement may persist for years after successful repair of atrial septal defect. Meyer and colleagues[106] performed serial M-mode echocardiograms in 51 children with isolated secundum atrial septal defect before and after surgery. They found there was an initial decrease in right ventricular size in the first three months after operation but that echocardiographic evidence of right ventricular dilation persisted in over 80% of these children for a period of up to 5 years. These results are corroborated by the data of Graham and colleagues, who performed preoperative and postoperative cardiac catheterization in three children with secundum atrial septal defects and found persistently elevated right ventricular volume 1 year after catheterization.[107]

Closure of atrial septal defects in childhood is often recommended to prevent supraventricular arrhythmias later in life. The incidence of chronic symptomatic postoperative arrhythmias is much lower in children after atrial septal defect repair than in untreated adults with large atrial septal defects. However, postoperative arrhythmias do occur in children who have undergone operative closure of secundum atrial septal defect. Bink-Boelkens and colleagues[108] reported a 23% incidence of postoperative arrhythmia in 204 children with secundum atrial septal defect. Sinus-node dysfunction was present in 39% and atrial flutter was present in 18% of the patients with arrhythmia. In 56% of the cases, dysrhythmia was first noted after discharge from the hospital. Atrial flutter developed in 9 of 15 of the children after the first postoperative year. Four patients (2%) required insertion of a pacemaker for treatment of bradycardia or a bradycardia–tachycardia syndrome postoperatively. Bricker and colleagues[109] have also noted that a small number (6 of 292, or 2%, in their series) of patients with atrial septal defect will require pacemakers for arrhythmias after surgery. In this regard, it is of note that Bharati and Lev have recently reported four cases of sudden death after atrial septal defect repair.[110] Surgical damage to the sinus node and fibrosis of conduction tissue were found.

Symptomatic arrhythmias are frequently present in adults after operation. These arrhythmias may persist after surgery or new arrhythmias may be caused by surgery. In some cases, surgical closure of atrial septal defect and relief of cardiac volume overload results in resolution of preoperative arrhythmias. Brandenburg and colleagues[111] found that atrial fibrillation was relieved by surgery in only 3 of 16 patients over 44 years of age. Results were better in patients who had paroxysmal supraventricular tachycardia. This arrhythmia did not recur postoperatively in 5 of 9 patients. Forfang and colleagues[112] found that 56 of 84 patients (67%) over 40 years of age with secundum atrial defect had arrhythmias. After surgical closure, 80% of their patients had arrhythmias at least once. However, only 21 of 55 patients (38%) followed into the late postoperative period had persistent arrhythmias that caused symptoms.

Bolens and Friedli[113] performed electrophysiologic studies in 18 children before and after surgical closure of a secundum atrial septal defect. They found that the preoperative A–H interval was prolonged, as was the corrected sinus-node recovery time and the atrioventricular nodal refractory period. Postoperatively, the A–H interval and the atrioventricular node refractory period decreased in length. The sinus-node recovery time decreased in 13 of 18 patients (72%). However, ectopic atrial rhythm developed postoperatively in 5 patients. The finding of shortening of the A–H interval correlates with the electrocardiographic finding of Bricker and colleagues that the P–R interval is shortened by surgical closure of an atrial septal defect.[109]

Patients with congestive heart failure due to left-to-right shunting and its consequent cardiac volume overload generally experience substantial relief of symptoms after closure of the defect. Weinberg and colleagues reported relief of symptoms in six of seven children with atrial septal defects who were in congestive heart failure.[114] Young noted relief of symptoms by surgical closure in three such children.[106] Relief can also be obtained by surgical closure in the occasional toddler or infant with atrial septal defect who experiences congestive heart failure,[115] though mortality may be increased in the presence of concomitant pulmonary hypertension.[116] Spangler et al. reported on a surgical series of 13 patients under 2 years of age with congestive heart failure secondary to an isolated secundum atrial septal defect.[115] Operative repair was performed in 12 patients without mortality and with relief of symp-

toms. However, no patient in this series had pulmonary artery hypertension.

Repair of atrial septal defect also relieves congestive heart failure in the adult patient. Rahimtoola et al. noted substantial improvement in congestive symptoms after surgical repair of 22 of 23 patients over 35 yr of age who had an atrial septal defect and a moderate to large left-to-right shunt.[103] Forfang et al. also noted resolution of symptoms of congestive failure after corrective surgery in patients over 40 yr of age.[112] Others have reported similar results.[117] Even patients 60 yr of age and older experience considerable relief of congestive symptoms after surgery, and operative repair can be performed with only a small increase in mortality in this age group.[118,119]

The mortality and morbidity of atrial septal defect repair are increased with pulmonary vascular disease. Rahimtoola and colleagues[103] reported a mortality of 24% (13 of 55) in patients with secundum or sinus venosus atrial septal defects with pulmonary artery pressure in excess of 60 mm Hg. Three of 35 patients with a pulmonary vascular resistance less than or equal to 8 units/m^2 died, and 10 of 20 patients with a pulmonary vascular resistance in excess of 8 units/m^2 died. More recently, Steele and colleagues[40] have described improved postoperative results in patients with isolated atrial septal defect and moderate degrees of pulmonary vascular obstructive disease. They found that 19 of 24 surgically treated patients with a pulmonary vascular resistance of between 7 and 15 units were alive at least 4 years after surgery. Eighteen of these patients had had substantial regression of symptoms. However, all four surgically treated patients with pulmonary vascular resistance in excess of 15 units/m^2 had suboptimal results. Two of these patients died in the immediate postoperative period and the two survivors had substantial progression of symptoms.

Several investigators have reported that repair of sinus venosus atrial septal defect is associated with an increased incidence of arrhythmias as compared with repair of secundum atrial septal defect. Clark and colleagues[120] found a preoperative incidence of sinus-node dysfunction of 18% in patients with sinus venosus atrial septal defect and 3% in patients with secundum atrial septal defect. Postoperatively, patients with sinus venosus atrial septal defect were found to have a 50% incidence of a sinus-node dysfunction, while patients with secundum atrial septal defect had a 31% incidence of sinus-node dysfunction. In Young's series,[105] 2 of 6 patients (33%) had chronic arrhythmias after repair of a sinus venosus atrial septal defect, whereas only 14% of his entire postoperative atrial septal defect group had chronic arrhythmias. Kyger and colleagues[121] noted an incidence of preoperative arrhythmia of 14% (15 of 109) in patients with sinus venosus atrial septal defect who underwent surgical closure. New postoperative arrhythmias were noted in 21% (23 of 109) of their patients. Most of these new arrhythmias (56%, or 13 of 23) resolved before discharge from the hospital. New tachyarrhythmias tended to resolve, whereas most bradyarrythmias persisted. However, Trusler and colleagues[122] found that only 3 of 29 children had symptoms related to arrhythmias after repair of sinus venosus atrial septal defect.

Obstruction to venous return at the superior vena caval–right atrial junction may occur after surgical repair of sinus venosus atrial septal defect.[123] Enlargement of this junction can be performed surgically, but should be performed carefully, because damage to the sinus node may be produced.

The risk of death from repair of coronary sinus atrial septal defect, either isolated or in association with a persistent left superior vena cava, is apparently low. Quaegebeur and colleagues reported on repair in eight such patients with no operative mortality or late deaths.[99] In many cases coronary sinus atrial septal defect is seen in conjunction with atrioventricular canal and other complex lesions. In these cases, the prognosis is principally determined by the associated anomaly. Because of the proximity of the atrioventricular node to the atrioventricular communication in coronary sinus atrial septal defect, atrioventricular block may be caused by surgical repair. Untreated coronary sinus atrial septal defect in association with persistent left superior vena cava is sometimes associated with cerebral embolization and abscess secondary to right-to-left shunting.

Patients with moderate and large secundum atrial septal defects who do not have surgical closure of the atrial septal defect generally do well without surgical treatment until the third decade of life, after which they tend to become progressively more symptomatic (see section on "Natural History"). However, because other disorders such as cancer and coronary artery disease supervene, only a fraction of patients born with an atrial septal defect of moderate or large size will actually die from the direct effects of the atrial septal defect. Thus in the absence of pulmonary hypertension, life expectancy in untreated isolated secundum atrial septal defects of moderate and large size may be as long as 50 to 60 years. Patients with small atrial septal defects have a good prognosis, and probably have nearly the same life expectancy as the general population.

PERSISTENT COMMON ATRIOVENTRICULAR CANAL DEFECTS

Atrioventricular canal defects include a range of malformations, a central feature of which is usually an atrial septal defect, and that involve, in addition to the atrial septum, the ventricular septum and one or both atrioventricular valves.[124,125] A number of terms have been applied to these malformations, including endocardial cushion defect, atrioventricular septal defects, canalis atrioventricularis communis, and persistent atrioventricular ostium.

Historical Aspects

Keith was aware of defects in the lower portion of the atrial septum and termed them foramen primum defects. He described them in his Hunterian lectures in 1909.[126] Abbott recognized both ostium primum atrial septal defects and common atrioventricular canal defects.[127] Rogers and Edwards concluded that these defects were similar morphologically.[128]

In 1956, Lillehei and colleagues reported the first successful repair of an atrioventricular canal defect, using cross-circulation.[129] In the same year Kirklin successfully repaired a partial atrioventricular canal defect through an atrial well.[130] The development of the pump oxygenator thereafter made repair of defects by open cardiotomy much more practical.

Further morphologic studies were stimulated by the rapid development of cardiac surgery. Wakai and Edwards performed an extensive review of pathological specimens with persistent common atrioventricular canal defect, noted the presence of associated defects, and also noted that the lesion was a serious one, as evidenced by the early age of demise of many of the patients that

they studied.[131] Lev described the location of the conduction system in relation to the atrioventricular canal defect in these patients.[132] In 1966 Rastelli and colleagues made a detailed description of the atrioventricular valve leaflets in patients with common atrioventricular canal defect.[133] Van Mierhop et al. performed extensive studies on cardiac embryogenesis that contributed greatly to understanding of the pathogenesis of these defects.[134] There have been many recent advances in the diagnosis and therapy of these defects. Rapid clinical identification and effective treatment are now possible in the great majority of patients.

Classification

There are a number of different types of atrioventricular canal defects and several methods for classification of these defects.[133,135,136] A distinction is usually made between partial and complete defects. Some authors use the term partial atrioventricular canal defect to indicate atrioventricular canal defects that have an interatrial communication but no interventricular communication and the term complete atrioventricular canal defect to describe atrioventricular canal defects that contain both an atrial and a ventricular septal defect. Others use the term partial atrioventricular canal defect to indicate the presence of separate mitral and tricuspid valve orifices and the term complete atrioventricular canal defect to indicate the presence of a common atrioventricular valve orifice. In this discussion we will use complete atrioventricular canal to indicate the presence of both atrial and ventricular septal defects and a common atrioventricular orifice. We will term all other cases of persistent common atrioventricular canal "partial" or "incomplete."

Embryologic Aspects

Atrioventricular canal defects appear to result primarily from abnormal development of the endocardial cushions.[17,18] In normal development the superior and inferior endocardial cushions grow together and fuse at approximately 5 weeks of age. Their fusion divides the common atrioventricular canal into two parts, the left and right atrioventricular canals. In patients with endocardial cushion defects, the superior and inferior cushions do not close completely. Because they do not close, they cannot fuse with the ostium primum, which normally grows inferiorly to meet them and close the atrial septum. Thus an interatrial communication is left at the lower portion of the atrial septum. This communication is often termed a persistent ostium primum defect, a description that may be something of a misnomer because the development of the ostium primum is not necessarily defective. In addition to causing an interatrial communication, the failure of fusion of the endocardial cushions results in an abnormally low position of the atrioventricular valves and an abnormally high position of the aortic valve, the basis for the characteristic "gooseneck" deformity. Though relatively small portions of the atrioventricular valves originate from the endocardial cushions, fusion of the left tubercles of the superior and inferior endocardial cushions must occur properly if the anterior leaflet of the mitral valve is to be formed normally. Since these cushions do not properly fuse in atrioventricular canal defects, most patients are left with an anterior and a posterior component to the anterior mitral valve leaflet.

Pathologic Aspects

General Features

Persistent common atrioventricular canal defects have a number of distinctive morphologic features, many of which are important physiologically and most of which must be considered in the surgical repair of the lesion.[133,135,136] Some of these features are seen in all atrioventricular canal defects. Others are a feature of only the complete defects. The following features are present to some degree in most atrioventricular canal defects[137–139]:

- The anterior or aortic leaflet of the mitral valve is abnormal in most hearts with atrioventricular canal defect. Anterior and posterior components of the leaflet are present, separated by a gap or "cleft."
- The septal leaflet of the tricuspid valve is abnormal in many cases of atrioventricular canal defect. As with the mitral valve, anterior and posterior components of the leaflet are present, separated by a gap or "cleft."
- The ventricular inlet septum is concave toward the atrium. Consequently, the ratio of the inlet distance (from the atrioventricular valve annulus to the ventricular apex) to the outlet distance (from the ventricular apex to the aortic valve) is substantially less than one in these patients. In normal subjects this ratio of distances is approximately one.
- The left ventricular outflow tract is not wedged between the two atrioventricular valves. Rather it is displaced anteriorly or "sprung." As a consequence, the left ventricular outflow tract is elongated and narrowed, giving the characteristic "gooseneck" appearance on anteroposterior cineangiograms.
- Because the left ventricular outflow tract is not wedged between the two atrioventricular valve orifices, the left and right atrioventricular valve attachments lie at the same level. In normal subjects, the atrioventricular valves are attached at different levels, with the insertion of the tricuspid valve displaced toward the apex of the heart. Hence there is a small area of septum, termed the atrioventricular septum, between the left ventricle and the left atrium. This septum is absent in persistent common atrioventricular canal defects, an absence that has led some authors to use the term "atrioventricular septal defect" instead of "persistent common atrioventricular canal defect."

The manner of attachment of the atrioventricular valve tissue determines whether or not a ventricular septal defect is present. In persistent common atrioventricular canal defects without a ventricular septal defect, the atrioventricular valves are attached to the crest of the ventricular septum, preventing interventricular communication. In patients who have a ventricular defect, the atrioventricular valves close above the deficient ventricular septum, leaving an interventricular communication.

Many cardiovascular structures are abnormal to variable degrees in patients with persistent common atrioventricular canal defects. Abnormalities in specific structures are described in more detail in the following paragraphs.

Atrial Septum

Most atrioventricular canal defects include an interatrial communication. These defects are often called ostium primum atrial septal defects. They lie at the lowest part of the atrial septum and are variable in size (but usually large in relation to cardiac size) depending on the amount of atrial septal tissue that is deficient in

addition to the atrioventricular septum. The lower edge of these defects is concave.

The remainder of the atrial septum may be formed normally, but often other abnormalities are present. The lower part of the limbus of the fossa ovalis may be absent. In addition to the ostium primum defect, other types of interatrial communications may be present in these patients. Associated secundum atrial defects are particularly common. It is possible for almost the entire atrial septum to be absent, in which case a "common atrium" exists, as discussed below.

Ventricular Septum

The basal portion of the ventricular septum is deficient in most hearts with persistent common atrioventricular canal. In hearts without a ventricular septal defect, the atrioventricular valve tissue attaches to the crest of the ventricular septum, preventing an interventricular communication. In hearts with a ventricular septal defect, this tissue does not attach along the entire length of the septum, creating a gap bounded superiorly by valve tissue and inferiorly by the crest of the septum.

From the right ventricular aspect, the ventricular septal defect seen in the atrioventricular canal defect lies in the uppermost part of the ventricular septum. It is bounded superiorly by the right aspect of the atrioventricular valve ring and is located posteriorly and inferiorly to the crista supraventricularis. From the left ventricular aspect, the defect is located in the outflow tract of the left ventricle and includes a substantial deficiency of the muscular septum adjacent to the anterior (aortic) leaflet of the mitral valve.

Separate ventricular septal defects of the muscular or perimembranous variety may exist in conjunction with the ventricular septal defect of the atrioventricular canal and may complicate diagnosis and therapy in these patients.

Isolated ventricular septal defects can exist in the inlet ventricular septum, located posteriorly and inferiorly to the crista supraventricularis and bounded superiorly by the ring of the tricuspid valve. Such defects are often referred to as ventricular septal defects of the atrioventricular canal type, though other features of persistent common atrioventricular canal may be absent.

Atrioventricular Valves

The hallmarks of the persistent atrioventricular canal defect are the abnormal atrioventricular valves. There are abnormalities in both the overall configuration and orientation of the valve apparatus and in the local structure of the atrioventricular valves. In both partial and complete forms of atrioventricular canal defect the atrioventricular valves lie in the same plane with respect to the base of the ventricular septum. By contrast, in the normal heart there is a small displacement of the plane of the tricuspid valve toward the apex. Additionally, whereas the annulus of the normal atrioventricular valves lie in one plane, the annulus of the atrioventricular valves in patients with persistent common atrioventricular canal defect is convex toward the cardiac apex.

In partial defects there are two separate atrioventricular valve annuli. In this situation the left and right atrioventricular valve leaflets are usually named according to the mitral and tricuspid valve components to which they correspond most closely. In complete atrioventricular canal defects there is a common atrioventricular valve. This common valve has a basic five-leaflet structure. There are two leaflets that straddle the interventricular septum and are tethered by chordae in both ventricles. These are called the anterior (or superior) and posterior (or inferior) bridging leaflets. Two leaflets are located in the right ventricle and roughly correspond to the anterior (or anterosuperior) and posterior (or mural) leaflets of the tricuspid valve. One leaflet is entirely contained within the left ventricle and is termed the left lateral (or mural) leaflet. The preceding valve-leaflet nomenclature is used here.

An alternative system of nomenclature has been developed by Kirklin and colleagues.[140] They note that the anterior bridging leaflet is usually divided into two portions by a commissure. They consider each of these portions to be a separate leaflet of the common valve. With their system, the valve leaflets in all persistent common atrioventricular canal defects, including partial defects, are named according to a six-leaflet concept. The posterior bridging leaflet in their system is termed the left inferior leaflet and the left lateral leaflet is given the same name as in the traditional system. The right anterior leaflet is designated as the right lateral leaflet and the right posterior leaflet is termed the right inferior leaflet. The left and right portions of the traditional anterior bridging leaflet are designated as the left and right superior leaflets, respectively.

In practice, there is wide variability in the atrioventricular valve morphology of this disorder. Some patients will have only four identifiable leaflets at autopsy, whereas others may have as many as seven. Furthermore, the leaflets are often deformed, with thickened midpoints and gnarled edges that coapt poorly. Additionally, the valve tensor apparatus (chordae and papillary muscles) is often severely abnormal, as will be discussed more fully below.

Incomplete Atrioventricular Canal Defects with No Interventricular Communication

Separate mitral and tricuspid valve annuli are usually present. The anterior (septal) leaflet of the mitral valve is composed of two components, which are usually of approximately equal size, separated by a gap or cleft. These two portions of the anterior leaflet attach to the crest of the ventricular septum by chordae tendineae and fuse with the septal leaflet of the tricuspid vale. This fusion prevents direct interventricular communication. The posterior (lateral, mural) leaflet of the mitral valve is usually normal.

The free edges of the components of the divided anterior leaflet attach to chordae tendineae that connect to the anterolateral or posteromedial papillary muscles of the left ventricle. The edges of the divided anterior leaflet that are facing each other do not usually attach to chordae tendineae. However, occasionally short chordae tendineae attach to the edges of the divided anterior leaflet, limiting its mobility and contributing to mitral valve insufficiency. The edges of the cleft anterior mitral valve are often thickened and irregular, causing poor coaptation with resultant mitral valvular insufficiency.

The tricuspid valve is usually abnormal also in partial forms of persistent common atrioventricular canal, with frequent absence of the anterior part of the septal leaflet and a widened anteroseptal commissure.

Transitional Forms of Atrioventricular Canal Defect

The terms "transitional" and "intermediate" were used by Wakai and Edwards to describe a group of malformations wherein a bridge of valvular tissue on the ventricular septal crest connected

the anterior leaflet with the septal extension of the posterior leaflet.[141]

Common Atrium

It is possible for almost the entire atrial septum to be absent. In these instance, at least one band of muscular tissue crosses the atrium as a vestigial atrial septum. These defects are nearly always associated with a cleft anterior leaflet of the mitral valve and a deficient summit of the ventricular septum.

Isolated Ostium Primum Atrial Septal Defect

Ostium primum atrial septal defects are characteristically associated with a cleft in the anterior leaflet of the mitral valve. A case of isolated ostium primum atrial septal defect with ostensibly normal atrioventricular valves has been described.[142] However, such defects must be extremely rare.

Complete Atrioventricular Canal Defect

In the complete form of atrioventricular canal defect there is a common atrioventricular orifice and a common atrioventricular valve. In most cases, both an ostium primum atrial septal defect and a ventricular septal defect of the atrioventricular canal type are present and are confluent. As has been noted, the common valve has an anterior leaflet that straddles or bridges the ventricular septum. Rastelli et al.[133] noted three major variations in the structure of this anterior bridging leaflet and classified complete atrioventricular canal defects accordingly. The technique of surgical repair differs for these three different forms of complete atrioventricular canal defect.

Divided, Septally Attached Anterior Common Leaflet

The anterior common leaflet is divided into two portions of approximately equal size in this type. One of these is located primarily in the right ventricle and one is located primarily in the left ventricle. The lateral part of each portion of the valve is attached to the anterior papillary muscle in the respective ventricle. Medially, the valve portions are attached to the crest of the ventricular septum by thin chordae tendineae that insert either on the crest of the ventricular septum or a few millimeters below it on the right ventricular side of the septum.

The interventricular communication in this type of defect is present above the crest of the ventricular septum, between the anterior and posterior bridging leaflets, at locations where the septum is bare of valvular tissue and through spaces that exist below these leaflets and between their chordae tendineae. At least part of the membranous septum is present in this form of complete atrioventricular canal defect, so that the ventricular septal defect does not extend to the aortic cusps.

As a consequence of the attachment of the left ventricular portion of the anterior common leaflet to the deficient ventricular septum, the apparent narrowing and elongation of the left ventricular outflow tract is accentuated.

Divided, Septally Unattached Anterior Common Leaflet

The anterior common leaflet is divided into two parts, neither of which is attached to the interventricular septum in the midline. Chordae tendineae from the midportions of the divided anterior leaflet are attached to a papillary muscle located in the right ventricle near the septum. Laterally, each portion of the valve is attached to the appropriate anterior papillary muscle.

An interventricular communication is present under the common leaflets. The ventricular septal defect extends to the aortic valve cusps. The left ventricular outflow tract is also narrowed and elongated with this type of defect.

Undivided, Septally Unattached Anterior Common Leaflet

The anterior common leaflet of this type is neither divided nor attached in its midportion to the septum or elsewhere. Rather, it "floats" above the ventricular septum. Laterally, the left and right portions of this common anterior leaflet are attached to the right and left anterior papillary muscles, respectively.

The interventricular communication lies below the common leaflets and extends to the aortic valve cusps. As with the other two types of complete atrioventricular canal defects, the left ventricular outflow tract is narrowed and elongated.

This third form of complete atrioventricular canal defect is most common in patients with major associated cardiac and/or extracardiac anomalies such as tetralogy of Fallot or Down's syndrome.

Titus and Rastelli[124] suggest that the three different forms of complete atrioventricular canal represent three different degrees of abnormal development of the anterior (superior) endocardial cushion with regard to its role in obliteration of interventricular communication in the embryonic heart and its role in formation of the anterior leaflet of the mitral valve and the septal leaflet of the tricuspid valve.

Piccoli and colleagues[135,136] accept the Rastelli classification groups, but do not agree with the concept of a common anterior leaflet that may be divided or undivided. Rather, they consider the traditionally termed common anterior leaflet to be composed of two leaflets. They call the left portion of the common anterior leaflet the superior bridging leaflet and they consider the right portion of this leaflet the anterosuperior leaflet of the tricuspid valve. The anatomy of the three Rastelli groups is explained in terms of differing degrees of bridging of the superior bridging leaflet with differing degrees of concomitant hypoplasia of the tricuspid anterosuperior leaflet. Kirklin and Barratt-Boyes also accept the Rastelli groups and provide a similar explanation of the anatomy based on their system of nomenclature.[143]

Posterior Common Leaflet

The posterior common leaflet, which is often rudimentary, is common to both ventricles. It is not usually divided into two distinct portions, and its edges are often thickened and curled. This leaflet is attached laterally by chordae tendineae to the posterior papillary muscles in the left and right ventricles. The posterior leaflet may attach in the midline to the muscular septum by short chordae tendineae.

Lateral Leaflets

The right and left lateral leaflets are analogous to the posterior leaflets of the tricuspid and mitral valves, respectively. They are usually well developed and attach to the anterior and posterior papillary muscles in the right and left ventricles in a normal manner.

Accessory Orifices

Accessory atrioventricular valve orifices are sometimes observed in association with atrioventricular canal defects.[144] Usu-

ally, all chordae tendineae that attach to such an accessory orifice converge and insert into a single papillary muscle. These accessory orifices generally do not cause hemodynamic abnormalities.

Papillary Muscles

The papillary muscles often have an abnormal configuration in persistent common atrioventricular canal defects.[145] In normal hearts the commissures and papillary muscles of the mitral valve are located at posteroseptal and anterolateral positions. In atrioventricular canal defects the papillary muscle groups are shifted laterally. On occasion there is only one papillary muscle group, in which case an ''iatrogenic parachute mitral valve'' will exist if the cleft in the anterior leaflet of the mitral vale is sutured closed.

Occasionally, two papillary muscles exist but the chordae tendineae from the anterior and posterior leaflets converge and insert almost entirely on the anterolateral muscle group. This abnormality is also potentially a parachute mitral valve.

Additionally, the right ventricular papillary muscles may be abnormal. In complete atrioventricular canal defects, the right medial papillary muscle may be located at an anomalous apical position or may be fused with the anterior papillary muscle to form an anomalous bifid anterior muscle.

Left Ventricular Outflow Tract

The left ventricular outflow tract in the persistent common atrioventricular canal defect is intrinsically narrow. However, physiologically important obstruction is unusual. When such obstruction occurs it may result from discrete membranes, from abnormally positioned papillary muscles, from atrioventricular valve tissue protruding into the left ventricular outflow tract, or from generalized severe hypoplasia of the left ventricular outflow tract.[146–148]

Left Ventricular Inflow Obstruction

Left ventricular inflow obstruction may occur with atrioventricular canal defects. Potential causes of obstruction are thickening of the valve leaflets, tethering of the ''cleft'' of the left atrioventricular valve to the septum, or narrowing of the entrance into the left ventricle, usually seen in conjunction with substantial right ventricular dominance.[146] Left ventricular inflow obstruction may also be caused by a supravalvular fibrous ring or cor triatriatum.[149]

Ventricular Dominance

Both left and right ventricular dominant forms of common atrioventricular canal occur.[137] Severe dominance of either ventricle substantially increases the risk of corrective surgery.[150]

The Conduction System

The defective atrioventricular septum in atrioventricular canal defect is associated with concomitant abnormalities in the atrioventricular conduction system, which have been demonstrated by pathological examination, and which have important surgical implications.[132,151,152] The atrioventricular node is displaced posteriorly from its usual relationship to the coronary sinus ostium. Frequently, these structures are directly adjacent. The undivided portion of the common bundle is shorter than normal. The course of the common bundle is closely related to the rim of the ventricular septum, especially at the posteroinferior rim. There is relatively early origin of the left bundle fibers and hypoplasia of the anteriorly directed left bundle fascicles. The posterior disposition of the conduction tissue is believed to account for the superior deviation of the mean QRS axis in the frontal plane with a counterclockwise QRS loop.

Acquired Cardiovascular Pathology Associated with Atrioventricular Canal Defect

Pulmonary Arteries

Patients with persistent common atrioventricular canal defects of the complete variety have a high risk of developing pulmonary vascular obstructive disease as they grow older.[153–156] Neufeld and colleagues demonstrated advanced pulmonary vascular disease (Heath–Edwards grades 3 and 4) in seven of eight patients with complete atrioventricular canal over age 1 year.[157] When pulmonary vascular disease is advanced, corrective surgery is contraindicated, since it is associated with substantially increased mortality and does not improve the prognosis of the patients. It is unlikely that pulmonary vascular disease will develop in childhood in patients with partial common atrioventricular canal defects though there is a small possibility that this will happen in later life.

Physiology

Intrauterine Physiology

Because of the proximity of the ostium primum atrial septal defect to the tricuspid valve it is possible that superior vena caval blood flow, which is usually directed through the tricuspid valve, will shunt across the atrial septal defect to the left ventricle, decreasing the oxygen saturation difference between the ascending and descending aorta in the fetus. If this were to happen, there would be a concomitant increase in the saturation of blood ejected by the right ventricle, increasing the P_{O_2} in the blood flowing to the pulmonary vessels and possibly affecting their development. If a large ventricular septal defect is present, shunting of additional right ventricular blood across the defect into the aorta could occur. This effect would further decrease the P_{O_2} in the ascending aorta and increase the P_{O_2} of blood perfusing the lungs.

Atrioventricular valve insufficiency could have an important effect on blood flow in the fetus. Since the blood is ejected directly from the left ventricle into the right atrium through the mitral cleft, the shunt is obligatory (i.e., not influenced by the pulmonary and systemic resistances). The shunt decreases the left ventricular stroke volume and increases the right atrial and right ventricular blood flow. Thus blood flow into the ascending aorta is diminished. The relative narrowing of the left ventricular outflow tract in the atrioventricular canal defect may further serve to diminish aortic blood flow.

Partial Atrioventricular Canal

In the absence of pulmonary stenosis or pulmonary vascular disease, there is predominant left-to-right shunting in patients with atrioventricular canal defects. When only an atrial septal defect is present without substantial left atrioventricular valvular insufficiency, the physiology is identical to that of an atrial septal defect with shunting primarily determined by the relationship of the pulmonary vascular resistances. When major left atrioventricular val-

vular insufficiency is present, there is an additional left-to-right shunt across the cleft mitral valve directly from left ventricle to left atrium, which has been termed "obligatory" because it is from a high- to a low-pressure chamber. This additional left-to-right shunt causes volume overload of both the left and right ventricles and is associated with heart failure in early life.

Complete Defects

When a large interventricular communication is present there is additional left-to-right shunting, usually associated with systemic pulmonary artery pressures in the absence of pulmonary stenosis. Left atrioventricular valve incompetence compounds the ventricular volume overload in these patients, who will often have symptoms caused by pulmonary congestion. When pulmonary vascular disease develops, as is likely in such patients, their symptoms may improve. When advanced vascular disease ensues in later life, the physiology is the same as in patients with Eisenmenger's syndrome with the additional volume overload imposed by left atrioventricular valve insufficiency.

Natural History

The natural history of atrioventricular canal defect depends primarily on the pathologic anatomy of the malformation.[158] In patients with only an ostium primum atrial septal defect and minimal insufficiency of the left atrioventricular valve, the clinical course is similar to that of patients with a large secundum atrial septal defect. Generally, these patients do well without treatment during infancy, childhood, and adolescence. During adulthood they have an increasing tendency to develop congestive heart failure, particularly as atrial arrhythmias develop.

Patients with ostium primum atrial septal defects and moderate to severe left atrioventricular valve insufficiency will develop congestive heart failure in early life with a consequently high morbidity and mortality if the atrioventricular valve insufficiency is pronounced. Otherwise they may survive until adulthood, when they experience increasingly severe symptoms.

Patients with complete atrioventricular canal defects generally develop severe symptoms of congestive heart failure in early infancy. They have frequent respiratory infections and poor weight gain.

Physical Examination

Appearance

Patients with partial atrioventricular canal defects and minimal mitral insufficiency usually appear normal in infancy and childhood. Patients with partial atrioventricular canal defects and substantial mitral insufficiency may manifest growth failure, and other signs of chronic congestive heart failure. Patients with complete common atrioventricular canal defects are usually symptomatic from early infancy, with such manifestations as poor physical development, hyperinflated thorax, bulging precordium, Harrison's grooves and mild or intermittent cyanosis. If there are no signs of chronic congestive heart failure in a patient with known complete common atrioventricular canal defect, pulmonary stenosis or pulmonary vascular obstructive disease should be suspected.

Down's syndrome, which is frequently associated with endocardial cushion defects, has a characteristic physical appearance.[159] Infants with this syndrome have flat facial profiles, oblique palpebral fissures, and a large protuberant tongue. The hands are generally short and broad, with a palmar simian crease, a short fourth finger, and a distal axial triradius. The skin is dry and distinctively pale. There are two distinctive ocular features. The most frequently seen is an inner epicanthic skin fold that inserts on the lower lid. Brushfield spots (speckled iris) are the second distinctive ocular feature. When Down's syndrome is seen in conjunction with the physical signs of chronic congestive heart failure, the coexistence of complete common atrioventricular canal should always be suspected.

Arterial and Jugular Venous Pulse

In partial endocardial cushion defect, mitral regurgitation is sometimes associated with a so-called water-hammer pulse, which is caused by the rapid ejection of a large left ventricular stroke volume. Patients with congestive heart failure may, however, have a small pulse volume. When mitral regurgitation is present the jugular venous pulse may have a dominant V wave, as the right atrium in these patients receives left ventricular systolic flow.[160]

Precordial Movement and Palpation

When mitral regurgitation is present in patients with partial endocardial cushion defect, a systolic thrill is often present. This thrill radiates toward the sternum. When a large left-to-right shunt is present, there is often a palpable impulse in the second and third left intercostal spaces, reflecting the presence of a dilated, pulsatile, pulmonary artery trunk. Sometimes the pulmonic component of the second heart sound is palpable as well. The right ventricular volume and pressure overload associated with complete atrioventricular canal defects is associated with a prominent systolic impulse or "heave" at the left sternal edge and in the subxiphoid area.

Auscultation

Complete atrioventricular canal defects may be associated with a variety of auscultatory manifestations, depending on the nature of the underlying pathologic physiology. Since one common atrioventricular valve is present, the first heart sound is usually single. When the atrioventricular conduction time is prolonged, as is often the case, the first heart sound will tend to be relatively soft. There is usually constant or fixed splitting of the second sound, though when severe pulmonary hypertension is present, this splitting will be narrow. Pulmonary hypertension is also generally associated with a loud pulmonic component of the second sound. A murmur of atrioventricular valve incompetence is frequently present.[161] This murmur is usually maximal at the left ventricular apex and often radiates toward the sternum rather than toward the left axilla, reflecting the predominance of left-ventricular-to-right-atrial shunting over left-ventricular-to-left-atrial shunting. When the ventricular septal defect is restrictive and there is substantial pressure gradient between the left and right ventricles, a separate murmur of ventricular septal defect may be present, most prominently heard at the lower left sternal border.

The auscultatory findings in ostium primum atrial septal defect are similar to those found in fossa ovalis defects with the addition of an apical holosystolic murmur, secondary to atrioventricular valve insufficiency, that radiates toward the sternum. A pulmonic

flow murmur is often present in the second left intercostal space. There is wide, fixed, splitting of the second heart sound.

Electrocardiogram

The most characteristic abnormality seen in atrioventricular canal defect is a superiorly oriented QRS frontal-plane axis with a counterclockwise depolarization pattern[162] (Fig. 60–8). Ongley and colleagues[163] analyzed the electrocardiograms of 30 patients with complete atrioventricular canal defects and 116 patients with partial atrioventricular canal defects whose diagnoses had been confirmed at surgery. The mean frontal-plane QRS axis was between 0° and −61° in 35 patients (30%) with partial atrioventricular canal defects and in 1 patient (3%) with complete atrioventricular canal defect. The axis was between −61° and −91° in 47 patients (40%) with partial atrioventricular canal defects and in 6 patients (30%) with complete atrioventricular canal defects. An axis between −91° and −151° was seen in 25 patients (22%) with partial atrioventricular canal defects and in 21 patients (70%) with complete atrioventricular canal defects. Three patients with partial atrioventricular canal defects (3%) and 1 patient with complete atrioventricular canal defect had a QRS axis between 90° and 180°. An indeterminate axis was present in one patient with complete atrioventricular canal defect and in six patients with partial atrioventricular canal defects. The mechanism of alteration of the frontal plane QRS axis in these patients is not due to ventricular hypertrophy, but rather is caused by abnormally positioned conduction tissue, which causes an abnormal cardiac activation sequence.[151] Body-surface and epicardial mapping techniques have demonstrated that activation of the left ventricular posterior wall takes place asynchronously.[164]

An additional electrocardiographic finding commonly associated with atrioventricular canal defects is a prolonged P–R interval.[163] Electrophysiologic studies have shown that this prolonged P–R interval is secondary to a delay in intra-atrial activation in many cases, rather than to a delay in atrioventricular nodal conduction.[69] The majority of patients show a normal P-wave axis, with an increase in either P-wave amplitude or width, suggesting left or right atrial enlargement. Patients with ostium primum atrial septal defects often have electrocardiographic signs of right ventricular hypertrophy, particularly an rsR′ pattern in the left precordial leads. Patients with complete atrioventricular canal defects also commonly exhibit electrocardiographic manifestations of right ventricular hypertrophy. Electrocardiographic suggestions of biventricular or left ventricular hypertrophy may also occur in these patients, particularly if mitral or atrioventricular valve insufficiency is severe.

Chest Roentgenogram

Cardiac enlargement is usually present on chest roentgenogram in patients with ostium primum or complete atrioventricular canal defects (Fig. 60–9). In particular, right atrial and right ventricular enlargement is often present. The enlarged right heart often displaces the left ventricle, making evaluation of left ventricular size difficult.

The main pulmonary artery is usually prominent, and if a large left-to-right shunt is present, there are usually increased pulmonary vascular markings. If severe pulmonary vascular disease is present, the distal pulmonary vessels may have a lucent, pruned appearance. Severe enlargement of the pulmonary trunk and left atrium may compress the left main-stem bronchus and cause atelectasis of parts of the left lung.

Echocardiogram

M-Mode

The M-mode echocardiogram in patients with atrioventricular canal defects will characteristically show apparent diastolic move-

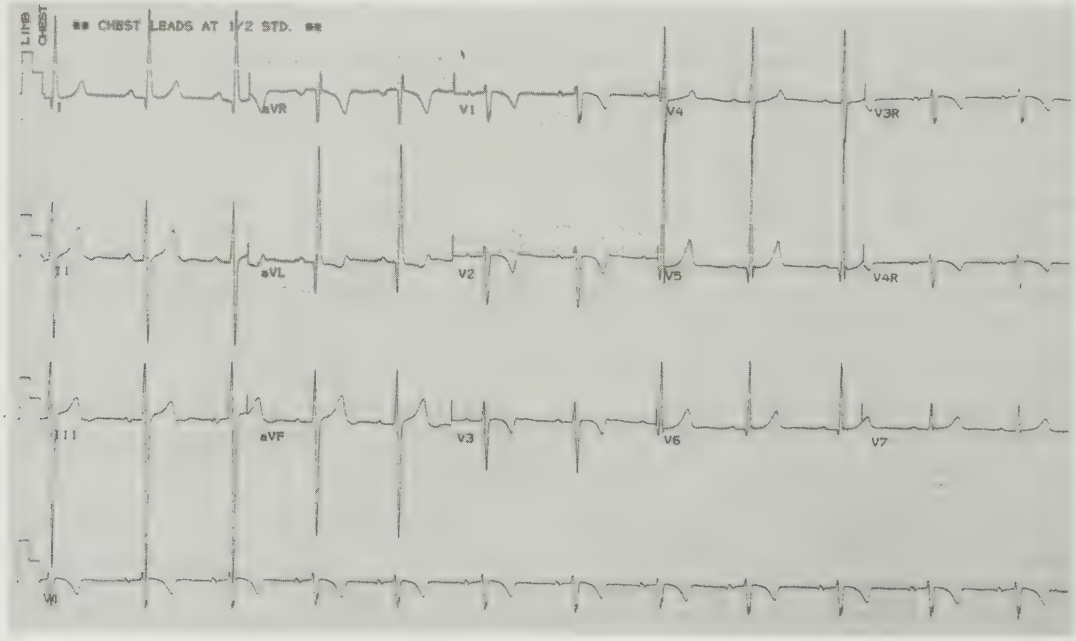

Fig. 60–8. Electrocardiogram from a 9-yr-old patient with a complete persistent atrioventricular canal defect and a pulmonary artery band. Note the position of the frontal-plane QRS axis.

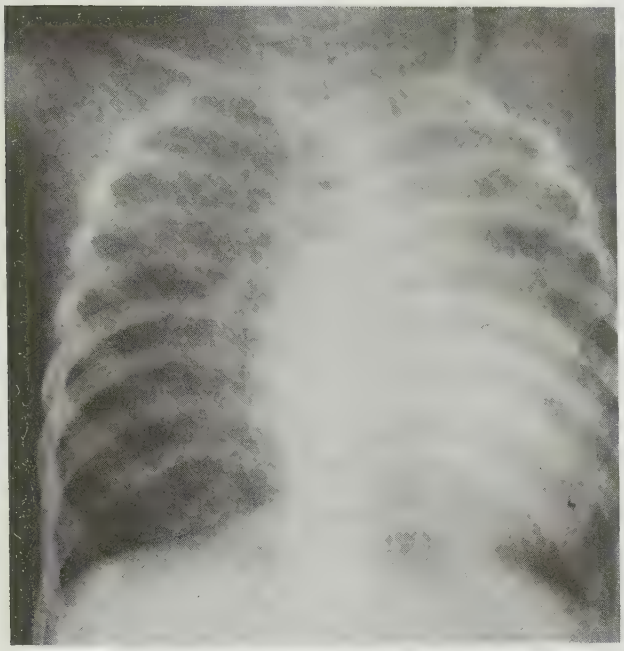

Fig. 60–9. Chest roentgenogram from an 8-mo-old patient with a complete persistent atrioventricular canal defect. Note the cardiomegaly and increased pulmonary vascularity.

ment of the mitral valve through the ventricular septum.[165,166] These findings are apparent in most atrioventricular canal deformities. M-mode echocardiography also reveals an enlarged right ventricle and paradoxical motion of the interventricular septum in many of these patients. Complete atrioventricular canal defects often exhibit gaps in ventricular septal echoes when scanning is performed from apex to base. Thus complete defects can sometimes be distinguished from partial defects. Although M-mode echocardiography is generally diagnostic in skilled hands, false-positive results can occur. In patients with right ventricular enlargement for other reasons, a medial transducer angulation may cause the mitral valve to appear to pass through the interventricular septum.

Two-Dimensional

The two-dimensional echocardiogram is highly reliable in identification of atrioventricular canal defects[167,168] (Fig. 60–10). The hallmark of the diagnosis is demonstration of an absent atrioventricular septum. In ostium primum atrial septal defects, the atrioventricular valve leaflets appear to originate from the crest of the ventricular septum. In complete atrioventricular canal defects, the bridging leaflets of the common atrioventricular valve are noted to cross the ventricular septum. If an atrioventricular septum is present, as evidenced by origin of the left- and right-sided atrioventricular valves at different levels, then the patient either has an isolated cleft mitral or tricuspid valve, or does not have an atrioventricular canal defect at all. The origin of both left and right atrioventricular valves at the same level does not necessarily imply that the patient has an atrioventricular canal defect.[169] Isolated inlet ventricular septal defects can exhibit this feature. However, in isolated inlet ventricular septal defect, the mitral valve is a normal mitral valve. In atrioventricular canal defects the left atrioventricular valve usually exhibits a cleft, which points toward the right atrium or right ventricle. Furthermore, as a consequence of the displacement of the left atrioventricular valve down the septum, the axis of the left atrioventricular valve opening is different in patients with atrioventricular canal defects and normal subjects. In atrioventricular canal defects, the left atrioventricular valve appears to open, on long-axis scans, at an angle pointing toward the lower portion of the ventricular septum and right ventricle. By contrast, in normal subjects, the axis of the left atrioventricular valve opening is toward the distal left ventricular free wall on long-axis scans.

Echocardiographers should use caution in making the diagnosis of atrioventricular canal defect in the presence of a large coronary sinus. In certain views, a large coronary sinus may appear to be an ostium primum atrial septal defect.

When the presence of an atrioventricular septal defect has been confirmed by two-dimensional echocardiography, it is necessary to complete the evaluation by assessing the detailed anatomy of the defect. When echocardiographic windows are adequate, skilled examination by experienced personnel should clearly define the following features of the defect.

Atrioventricular Valve Morphology. It is important to distinguish between defects with a common atrioventricular valve orifice and defects with two anatomically separate atrioventricular valves. This can be done best in the short-axis view. In complete atrioventricular canal defects, the anterior and posterior bridging leaflets are separate and not joined across the atrioventricular junction. In partial atrioventricular canal defects, these leaflets have fibrous continuity. Intermediate forms of atrioventricular canal defects can be identified echocardiographically in which this fibrous continuity is either a very thin strand or is not present across one of the bridging leaflets.

When separate atrioventricular orifices are present, both left and right atrioventricular valves are trileaflet structures. The left atrioventricular valve has a cleft or commissure that points toward the right atrium and right ventricle, as noted, and two commissures that point anterolaterally and posterolaterally. The right atrioventricular valve also has three commissures, pointing roughly anteriorly, posteriorly, and laterally. When a common atrioventricular orifice is present, common anterior and posterior atrioventricular valve leaflets are present that bridge the ventricular septum. These leaflets may either attach to the ventricular septum or float over the septum. As Rastelli[133] noted, three major groups of common atrioventricular canal defects can be identified based on the mode of attachment of the common anterior leaflet. The common anterior leaflet may be divided into two portions that attach to the crest of the ventricular septum, it may be divided into two portions that attach to a papillary muscle situated in the right ventricle near the septum, or it may be undivided and unattached to the septum. Careful echocardiographic investigation of the anterior bridging leaflet, particularly in short-axis cuts, can determine the attachments of the common anterior leaflet and thus enable noninvasive classification of the defect. The attachments of the posterior bridging leaflet should also be defined.

The two-dimensional echocardiogram can also demonstrate the presence of atrioventricular valve thickening. Thickened and gnarled atrioventricular valves are common in complete atrioventricular canal defects, and the presence of such deformities may complicate surgical repair. The total amount of usable atrioventricular valve tissue is also important surgically. As yet, no eval-

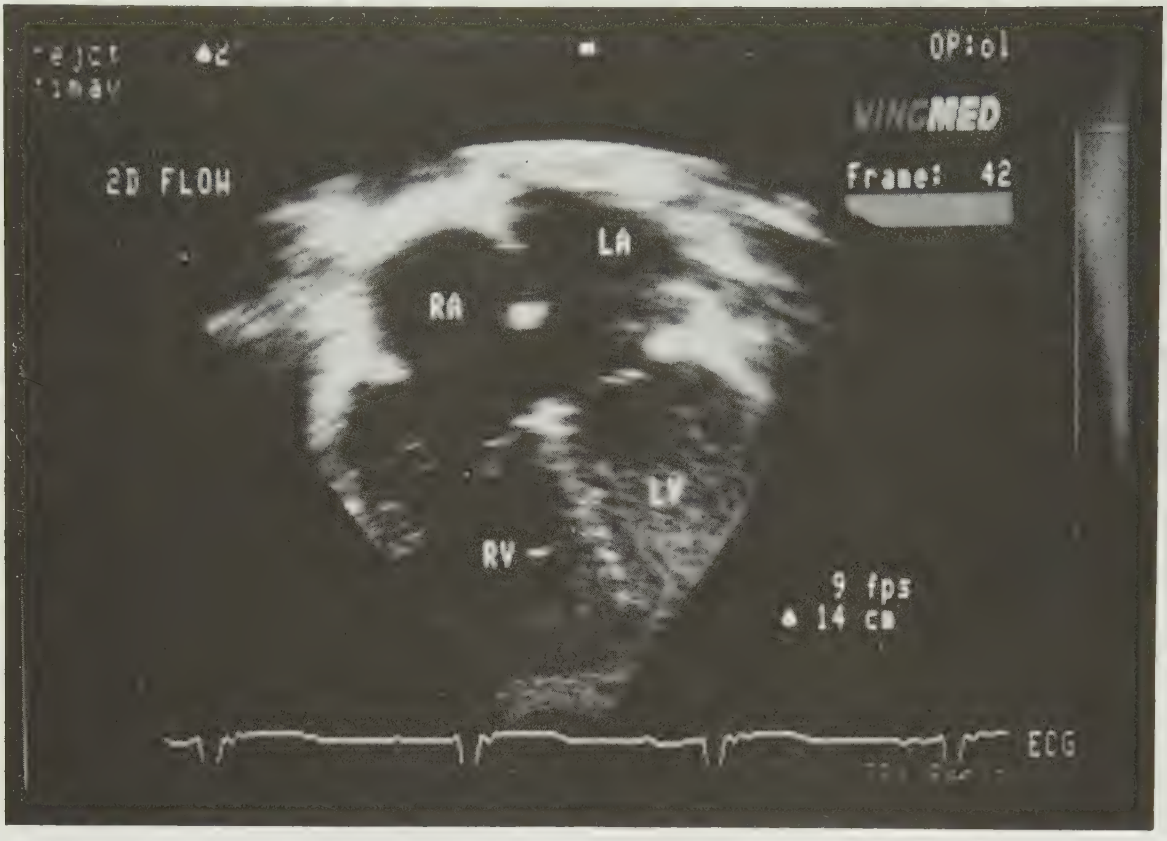

Fig. 60–10. Two-dimensional echocardiogram (apical four-chamber view, anatomical orientation) demonstrating a complete atrioventricular canal defect. RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle.

uation of this parameter has been made, but such an evaluation may be possible with two-dimensional echocardiography.

Occasionally, accessory atrioventricular valve orifices are present in conjunction with atrioventricular valve defects. These accessory orifices can be identified with two-dimensional echocardiography.

Presence of a Ventricular Component. The apical four-chamber view will demonstrate the presence or absence of a ventricular component to the atrioventricular canal defect. The ventricular component may be small and consist only of interstices between atrioventricular attachments to the crest or side of the ventricular septum. However, the ventricular septal defect can also be intermediate in size or quite large. It is important to define the size of the ventricular component of the atrioventricular canal as well as to rule out the presence of additional muscular ventricular septal defects.

Papillary Muscle Locations and Attachments. The papillary muscle attachments of the atrioventricular valve or valves should be defined in atrioventricular canal defects. It is particularly important to define atrioventricular valve attachments in the left ventricle.[170] The left ventricular papillary muscles are often closer together in patients with atrioventricular canal defects than in normal subjects. Sometimes only one left ventricular papillary muscle exists. Rarely, there are two distinct left ventricular papillary muscles but atrioventricular valve attachments to only one of these muscles. If the cleft of the left atrioventricular valve is closed surgically in either case, an iatrogenic parachute mitral valve will be created, with serious potential adverse consequences.

Atrial Septum. The size of the primum atrial septal defect should be determined. Scans from the subcostal view should facilitate this determination as well as the identification of additional atrial septal defects (secundum, sinus venosus) or common atrium.

Relative Chamber Sizes. The presence of left or right ventricular dominance is usually readily apparent on the echocardiogram, and is important from a prognostic standpoint.

Left Ventricular Outflow. The left ventricular outflow tract is narrowed in atrioventricular septal defects. Occasionally, it is obstructed by subaortic diaphragms, by anomalous left ventricular papillary muscles, or by fibrous "tissue tags." These obstructive lesions can usually be identified by careful echocardiographic examination. The aorta should be carefully examined in all patients with atrioventricular canal defects, as interrupted aortic arch and coarctation are frequent lesions. Doppler echocardiography can quantitate obstruction accurately when it is present.

Right Ventricular Outflow. Infundibular obstruction may be associated with atrioventricular canal defects, and usually has major surgical and prognostic implications. Thus careful echocardiographic evaluation of the right ventricular outflow tract is of major importance. As with the left ventricular outflow, Doppler studies are useful here to quantitate obstruction. The size of the distal pulmonary arteries should be determined echocardiographically when possible, as it usually is in infants and young children.

Ductus Arteriosus. The presence or absence of a patent ductus

arteriosus should be determined echocardiographically. A large patent ductus arteriosus may cause severe symptoms. It is important to know about the presence of even a small patent ductus arteriosus before considering cardiopulmonary bypass. Doppler echocardiography is often of great assistance in determining patency of the ductus arteriosus in these patients, particularly when pulmonary artery pressures are low. Then a continuous left-to-right shunt through the ductus is easily identified by two-dimensionally directed or color Doppler echocardiography. In patients with elevated pulmonary artery pressures, Doppler confirmation of ductal patency is more challenging because the left-to-right shunt is often phasic rather than continuous and may be detectable in only a small region of pulmonary artery.

Pulmonary Venous Connections. Total or partial anomalous pulmonary venous connection may occur in conjunction with atrioventricular canal defects. These lesions often have major prognostic importance and may greatly complicate surgical repair.

Systemic Venous Connections. Anomalies of systemic venous connections, such as persistent left superior vena cava and azygous continuation of the inferior vena cava are often important surgically and should be identified echocardiographically.

Visceral and Atrial Situs. Atrioventricular canal defects are frequently seen in conjunction with right and left isomerism. It is particularly important to identify right isomerism, since it is usually associated with asplenia, which requires antibiotic prophylaxis to prevent overwhelming infection.

Ventricular Function. Qualitative and quantitative estimates of ventricular function are readily made with echocardiography, and should be obtained.

Doppler

Doppler echocardiography can contribute substantially to the evaluation of atrioventricular canal defects. Pulsed Doppler is especially useful in the detection of left and right ventricular outflow obstruction and the presence of a ductus arteriosus. Pulsed Doppler examination also facilitates identification of atrioventricular valve regurgitation and has been employed to quantitate the degree of atrioventricular valve regurgitation.[171] As with other defects, pulsed Doppler echocardiography can provide relatively accurate estimates of pulmonary-to-systemic blood flow.

Continuous-wave Doppler is useful in quantitating pressure gradients. When a ventricular defect is present, the instantaneous pressure difference between the right and left ventricles can be determined using the modified Bernoulli formula. Similarly, pressure gradients across the left and right ventricular outflow tracts can be quantitated. Continuous-wave Doppler studies are particularly helpful in the followup of patients who have undergone pulmonary artery banding.[172] When pulmonary insufficiency is present, estimates of pulmonary artery diastolic pressure can be obtained. Similarly, estimates of pulmonary artery pressure can be made by quantitating the velocity of flow across the ductus arteriosus and measuring the systemic arterial blood pressure.

When tricuspid valve insufficiency is present, it is in principle possible to obtain estimates of right ventricular pressure. However, since a high-velocity left-ventricular-to-right-atrial flow of blood is often present in these patients, and since this flow may have a similar direction to the jet of tricuspid insufficiency, quantitation of the velocity of tricuspid valve insufficiency should be made with caution. Color Doppler identification of jet direction may be helpful in this regard.[173] Since multiple high-velocity jets of blood flow are frequently present in these patients, two-dimensional direction of continuous-wave Doppler beams should be used whenever possible, to avoid misidentification of the blood flow jets.

Color Doppler is also useful for determining the location and roughly quantitating the degree of atrioventricular valve insufficiency in these patients (Fig. 60–11). Additionally, color Doppler may also facilitate examination of patients for left and right ventricular outflow tract stenosis, for patent ductus arteriosus, and for multiple ventricular septal defects.

Radionuclide Angiography

Radionuclide angiography has been used to evaluate anomalous systemic venous connections. It may be useful in determining systemic-to-pulmonary venous flow ratios when atrioventricular valve insufficiency is absent or minimal.

Nuclear Magnetic Resonance

A major feature of atrioventricular canal defects, deficiency of the atrioventricular septum, is readily visualized with standard nuclear magnetic resonance imaging techniques.[174] In normal subjects as well as in patients with atrioventricular canal defects, the atrioventricular septum is best delineated by an imaging plane perpendicular to the axes of the lower atrial septum and the inlet ventricular septum. Such a plane demonstrates all four chambers of the heart, and is often termed the four-chamber view.

Because of the relatively thin structure and rapid motion of the atrioventricular valves, the atrioventricular valve anomalies associated with atrioventricular canal defects are difficult to characterize properly with current available nuclear magnetic resonance techniques. However, cine nuclear magnetic resonance methods show promise for detection and quantitation of the atrioventricular valve insufficiency often associated with the structural atrioventricular valve defects. Furthermore, nuclear magnetic resonance imaging can define many of the congenital cardiovascular abnormalities often associated with atrioventricular canal defects, such as coarctation of the aorta, pulmonary artery stenosis, pulmonary and systemic venous anomalies, and relative ventricular hypoplasia. Particularly in older patients, these associated anomalies may be difficult to define by other noninvasive techniques.

Cardiac Catheterization

Atrioventricular canal defects can be suspected at cardiac catheterization when the catheter course across the atrial septum is low. In many cases, because of the anatomy of these defects and the associated left-ventricular-to-right-atrial shunting, it is relatively difficult to maneuver the catheter into the right ventricle and out the pulmonary artery, as it tends either to pass into the left ventricle or flip back into the right atrium. Counterclockwise rotation with gradual movement of the catheter tip up the ventricular outlet septum will often succeed in such cases.[3] Balloon catheters can be used if other methods fail, but they are generally not recommended for angiography because of their relatively small lumens and tendency to recoil during injection. Oxygen saturation and hemodynamic findings in partial atrioventricular canal defect are generally similar to those obtained with catheterization of a secundum atrial septal defect.[175] Complete atrioventricular canal defects have these oxygen saturation and hemodynamic findings plus those of a ventricular septal defect.[176] It should be appreciated

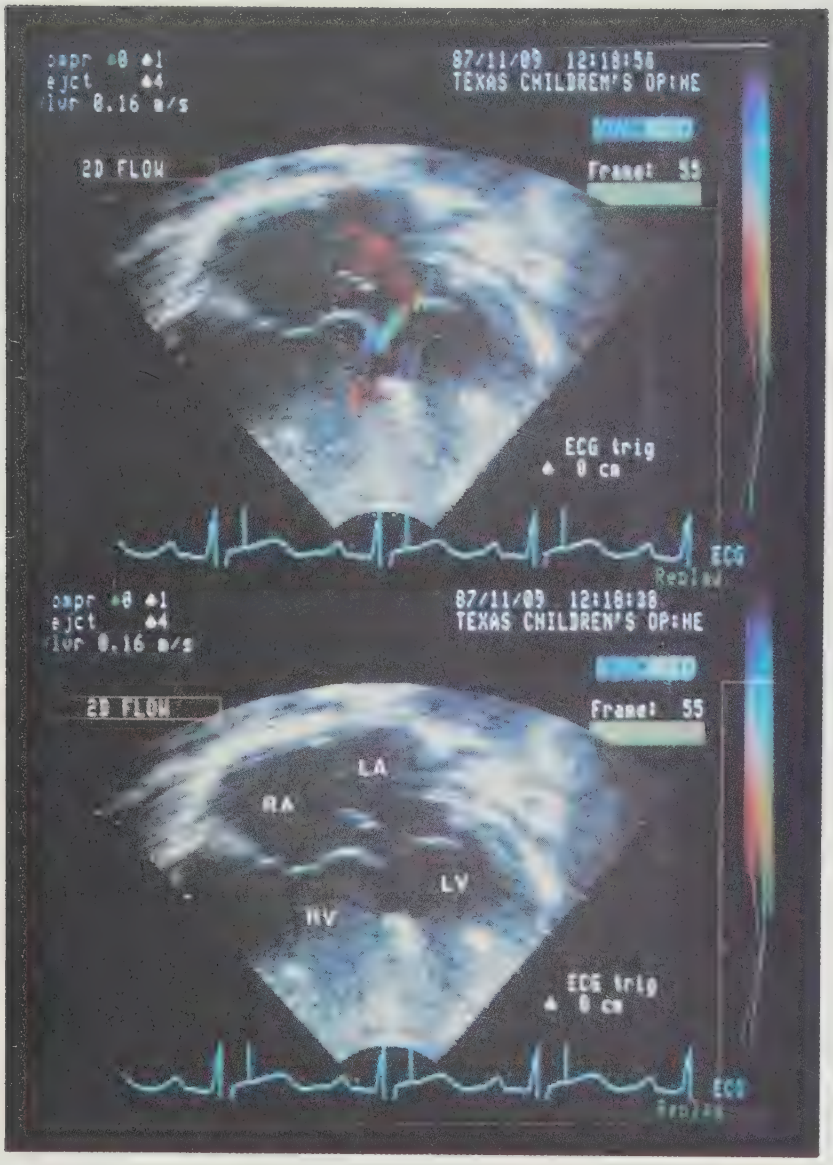

Fig. 60–11. Color Doppler study of a complete atrioventricular canal defect (apical four-chamber view, anatomical orientation). Top panel shows insufficiency from left portion of atrioventricular valve as greenish-yellow jet. RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle.

that calculation of pulmonary and systemic blood flow by the Fick method in these patients can be subject to errors and should be interpreted with caution. Estimation of systemic blood flow by this technique is dependent on obtaining a true mixed venous sample. When no intracardiac septal defects are present, pulmonary artery saturation provides an accurate estimate of the mixed venous oxygen saturation. In atrioventricular canal defects, oxygen saturation in the superior vena cava must be used, which may not represent the true mixed venous saturation. Similarly, estimation of pulmonary blood flow may be in error. A small pulmonary arteriovenous oxygen saturation difference may be present, in which case any variation in oxygen saturation among the pulmonary veins will lead to errors in the calculation. Errors will also be incurred if the patient is breathing an elevated concentration of oxygen and the effect of dissolved oxygen is not allowed for in the calculation. Estimates of systemic blood flow by indicator dilution curves will not be accurate in the presence of the usual left-ventricular-to-right-atrial shunt in these patients.

From the above considerations it follows that calculated pulmonary resistance values in these patients should be carefully evaluated. A number of authors suggest that evaluation of pulmonary vascular resistance while breathing 100% oxygen and after tolazoline injection should be performed if initial estimates indicate the presence of elevated pulmonary vascular resistance. Others suggest that patients should be intubated for evaluation if upper airway obstruction, with consequent carbon dioxide retention, is present at the time of cardiac catheterization. Patients with Down's syndrome often have some degree of upper airway obstruction from enlarged tonsils and adenoids. Calculated pulmonary vascular resistance values may improve markedly in these patients when the obstruction is relieved.[177]

Park and colleagues reported the results of cardiac catheterization in 53 patients with partial atrioventricular canal defects.[178] Patients with major associated cardiovascular anomalies such as coarctation were excluded from their series. Patient ages ranged from 2 months to 53 years, with a mean of 11 years. Systemic

arterial saturations while breathing room air were available in 41 patients. Arterial saturation was 95% or over in 25 of these patients and between 90 and 94% in 15. Only one patient had an arterial saturation between 80 and 89% while breathing room air. Mean arterial saturation for the group was 95%. Thus substantial systemic desaturation seems to be unusual in partial atrioventricular canal defect. Pulmonary resistances were less than 5 units in 40 of the patients. Two patients had mildly elevated resistances (6.2 and 7.5 units). Pulmonary-to-systemic blood-flow ratio was greater than 2:1 in 38 of the patients. Right-to-left shunting was demonstrable in 40 of the patients, but the average amount of the right-to-left shunt was only 9%. The maximum right-to-left shunt encountered was 28%.

Park and colleagues also reported the results of cardiac catheterization in 48 patients with complete atrioventricular canal defect.[178] Patient ages ranged from 2 days to 25 years. Systemic arterial saturations measured while breathing room air were available in 18 patients without pulmonary vascular disease. Thirteen of these patients had arterial saturation of less than 94% but greater than 89%. Two patients had arterial saturation of between 80 and 89%. Only three patients had an arterial saturation greater than or equal to 95%. Mean systemic arterial saturation for the group was 92%. Systemic arterial saturations measured while breathing room air were also available in 19 patients with pulmonary vascular disease. Six patients had saturations between 90 and 94%, but nine patients had saturations between 80 and 89% and four had saturations less than or equal to 79%. Mean arterial saturation for the group was 84%. Thus slight systemic arterial desaturation occurs in patients with complete atrioventricular canal defects in the absence of pulmonary vascular disease, but substantial systemic arterial desaturation is frequent in the presence of pulmonary vascular disease. In the patients without pulmonary vascular obstructive disease, the average pulmonary-to-systemic blood-flow ratio was greater than 2:1. Small right-to-left shunts were demonstrated by indicator dye dilution curves in 15 of 19 patients. In patients with complete atrioventricular canal defects and pulmonary vascular obstructive disease, right-to-left shunts were present in all patients, and the average amounts of left-to-right and right-to-left shunting was nearly equal at 38% and 39%, respectively.

Angiography

Selective left ventricular angiography in the anteroposterior projection demonstrates an elongated left ventricular outflow tract, with an abnormally low insertion of the anterior leaflet of the left atrioventricular valve, deficiency in the diaphragmatic wall of the left ventricle, and a disproportionately short inlet septum as compared with the outlet septum (Fig. 60–12). This combination of characteristics is diagnostic of an atrioventricular canal defect and is termed the ''gooseneck'' deformity.[179,180] The appearance of this deformity depends on left ventricular origin of the aorta. In the presence of double-outlet right ventricle the ''gooseneck'' may be difficult to recognize.

A thorough angiographic assessment of atrioventricular canal defects includes the following:

- Determination of the existence and size of ventricular components of the atrioventricular canal defect
- Determination of whether there is a common atrioventricular valve orifice or two separate atrioventricular valves
- Determination of the mode of connection of a common atrioventricular valve (balanced, left dominant, right dominant)

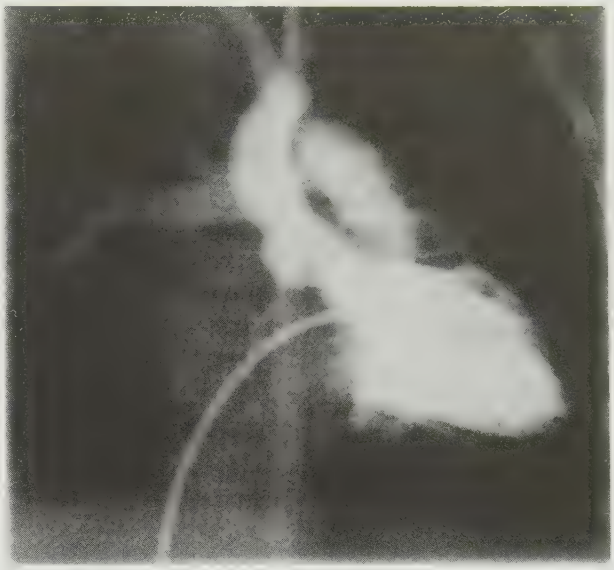

Fig. 60–12. Frame from a cineangiogram taken in the posteroanterior projection after injection into the left ventricle. Note the ''gooseneck'' deformity of the left ventricular outflow tract.

- Evaluation of the function of the atrioventricular valves
- Determination of the existence and size of atrial components of the atrioventricular canal defect
- Evaluation of the left ventricular outflow tract
- Evaluation of the right ventricular outflow tract and pulmonary arteries
- Detection of associated anomalies, such as anomalous pulmonary and systemic venous connections, patent ductus arteriosus, coarctation, and heterotaxia

Accomplishment of these objectives will usually require several contrast injections. Left ventricular injection into the hepatoclavicular or four-chamber view is the best method for evaluation of the inlet ventricular septum and for excluding apical muscular ventricular septal defects[90,181] (Fig. 60–13). Direct recognition of separate atrioventricular valve orifices or a common atrioventricular valve orifice is possible with this view. The mode of connection and the function of the left atrioventricular or common atrioventricular valve can also be evaluated from a left ventricular injection in the four-chamber view. The atrial septum is best assessed by an injection at the orifice of the right upper pulmonary vein in the hepatoclavicular position.[90,181] The size of the ostium primum atrial septal defect can be determined and the presence of additional secundum or sinus venosus atrial septal defects can be identified (Fig. 60–14). When there is a question about obstruction of the left ventricular outflow tract, left ventricular injection in the long-axis oblique projection will clearly demonstrate the left ventricular outflow tract along its axis. The right ventricular outflow tract and pulmonary arteries are best demonstrated by direct injection into the right ventricle or its outflow tract in the sitting-up or cranially angulated anteroposterior projection.[182] Patent ductus arteriosus, coarctation, and anomalous pulmonary venous connections are often associated with atrioventricular canal defects and can have deleterious effects if not identified before surgery. Additional contrast injections into the aorta and pulmonary arteries may be necessary to exclude these lesions.

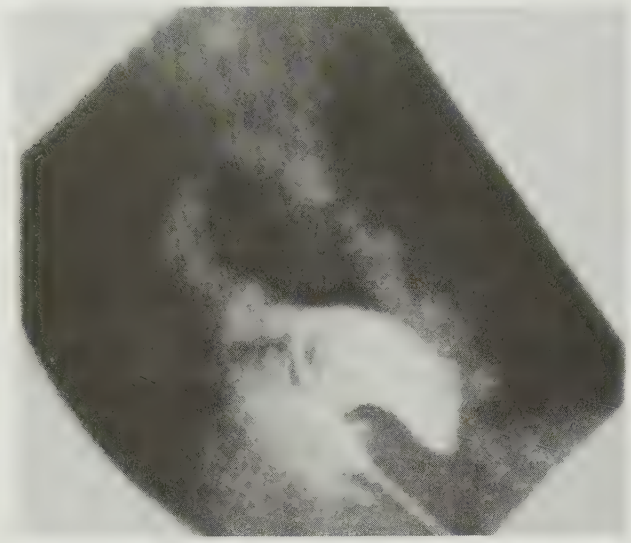

Fig. 60–13. Frame from a cineangiogram taken in the hepatoclavicular projection after injection into the left ventricle in a patient with complete atrioventricular canal defect. Note the large ventricular septal defect.

Angiographic definition is best when relatively large amounts of contrast are delivered rapidly through a large-bore catheter. This is particularly true in the presence of large left-to-right shunts, which rapidly dilute contrast delivered to the ventricles or pulmonary arteries. Since only a limited number of contrast injections are clinically feasible during a given study, noninvasive studies and prior angiographic examinations should be reviewed before catheterization so that optimal use of the available injections can be made. Digital angiography should prove to be of great assistance in this regard, because it requires substantially less contrast material. Nonionic contrast media should be useful in facilitating angiographic examinations in these patients.

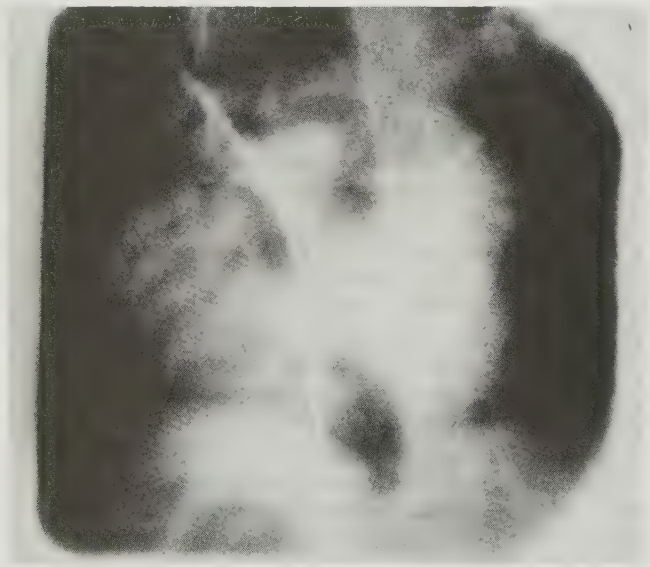

Fig. 60–14. Frame from a cineangiogram taken in the hepatoclavicular projection after injection at the orifice of the right upper pulmonary vein in a patient with a primum atrial septal defect. Note the low position of the defect in the atrial septum.

Electrophysiology

Electrophysiologic studies in preoperative patients with atrioventricular canal defects have demonstrated a prolonged intraatrial activation time with normal His–Purkinje conduction intervals. Twenty-one patients with atrioventricular canal, aged 3 months to 11 years, were evaluated preoperatively by Jacobsen and colleagues.[183] The high-right-atrial-to-low-right-atrial conduction time was prolonged in 15 of 18 patients (mean, 57 ± 20 msec) and the low-right-atrial-to-His-bundle conduction time was normal in 16 of 17 patients (mean, 82 ± 30 msec).

Nine patients with atrioventricular canal defects were studied by Jacobsen and colleagues after corrective surgery. High-right-atrial-to-low-right-atrial conduction time was prolonged in three of five patients. The low right-atrial-to-His-bundle conduction time was prolonged in two of seven patients, and one had acquired complete atrioventricular block in the His bundle. A prolonged His–Purkinje conduction time was found in two of eight patients. The site of prolongation of atrioventricular conduction could not be determined from the surface electrocardiogram in these patients. Fournier and colleagues[184] have obtained similar results preoperatively and postoperatively in patients with atrioventricular canal defects.

Treatment

Recommendations for treatment are dependent on the anatomic characteristics of the atrioventricular canal anomaly and on the state of the pulmonary vasculature. A central objective of treatment in these patients is to avoid development of pulmonary vascular obstructive disease.

When heart failure and associated pulmonary congestion are present, anticongestive measures such as diuretics and digoxin are indicated. Long periods of fluid restriction are generally counterproductive in small infants, since such restriction deprives them of calories needed for growth. Hydralazine has been shown to reduce the magnitude of left-to-right shunting in the short term in infants with atrioventricular canal defects,[185] but no long-term experience with the drug has been reported. Most cardiologists do not favor prolonged medical therapy in young patients without fixed pulmonary vascular obstructive disease if their symptoms are refractory, but rather refer them for surgical therapy when such therapy is feasible. Patients with an ostium primum atrial septal defect, separate atrioventricular valves, no ventricular defect, and minimal atrioventricular valve insufficiency generally are asymptomatic during infancy and childhood. Because repair of ostium primum atrial septal defect is associated with a greater potential morbidity than repair of a secundum atrial septal defect, many cardiologists do not recommend surgery at any age if cardiomegaly is absent, which usually is the case when atrioventricular valve insufficiency is mild and the pulmonary-to-systemic flow ratio is less than 2:1. Infants with partial atrioventricular canal defects that are symptomatic almost invariably have severe atrioventricular valve regurgitation. Pulmonary artery banding generally does not help these patients. Therefore corrective surgery with mitral valvuloplasty and atrial septal defect closure is usually recommended. Asymptomatic patients with ostium primum atrial septal defects

that do exhibit substantial cardiomegaly are usually referred for elective surgical repair when they near school age.

Patients with complete atrioventricular canal defects who do not have associated right ventricular outflow obstruction, generally have pulmonary pressures near systemic levels, and pulmonary vascular disease usually develops after the first year of life. Therefore either banding or corrective surgery during infancy is recommended in these patients.

Complete atrioventricular canal defects may be treated by pulmonary artery banding in infancy, followed by corrective surgery at an older age. Banding is most successful when high pulmonary blood flow from a large left-to-right shunt is present. In these cases, distal pulmonary artery pressure can be reduced to nearly normal levels and heart failure can be relieved.[186] However, banding may not result in substantially decreased distal pulmonary artery pressures if pulmonary vascular resistance is increased. Infants that do not have elevated pulmonary blood flow will not benefit from banding through a reduction in heart failure. Thus infants with atrioventricular canal defects and balanced or predominantly right-to-left shunting often do not improve symptomatically. When atrioventricular valve insufficiency, or an obligatory left-to-right shunt from left ventricle to right atrium, is the primary cause of cardiac volume overload, pulmonary artery banding will not relieve heart failure and may make it worse by increasing ventricular afterload. Pulmonary artery banding can distort the pulmonary arteries and thus complicate subsequent corrective surgery. Fisher and colleagues have obtained ventricular volume data suggesting that both right and left ventricular hypoplasia may be produced by pulmonary artery banding in patients with atrioventricular canal defects.[187]

Corrective surgery can now be performed even in early infancy.[188] There are several variants of the corrective surgical procedure.[140] Some surgeons use a single Dacron patch to close the atrial and ventricular components of the defect.[189] The right and left portions of the common atrioventricular valve are then resuspended from the patch. Other surgeons prefer to use a two-patch technique, and sandwich the leaflet tissue between the two patches.[190] The method of repair of the left atrioventricular valve also is controversial. Many agree with Carpentier that the left atrioventricular valve in these patients is best left as a trileaflet structure and that repair of the cleft should only be attempted as necessary to prevent postoperative regurgitation.[191] Others believe that it is best to attempt to reconstruct an approximation of a normal mitral valve.[192] Because of the highly variable anatomy of the defects, many aspects of each repair must be individualized. Particular attention should always be paid to ensuring a good left ventricular outflow.

Repair in the presence of right ventricular outflow obstruction (associated tetralogy of Fallot) is more complicated because it entails concomitant relief of infundibular and valvular pulmonic stenosis in addition to atrioventricular canal repair.[193] Additionally, the subaortic location of the ventricular septal defect in this combination of defects increases the technical difficulty of achieving appropriate division of the common atrioventricular valve, while maintaining a clear route from the left ventricle to the aorta. Fortunately, repair can usually be delayed until childhood in patients with obstruction to right ventricular outflow, since their pulmonary vasculature is protected by the obstruction. Patients symptomatic in infancy from low pulmonary blood flow can obtain effective relief from an aorticopulmonary shunting procedure.

The presence of left ventricular outflow obstruction also complicates repair of atrioventricular canal defects and increases risk, although successful corrective surgery can be accomplished with moderate degrees of obstruction.[194] Successful repair can also be accomplished when atrioventricular canal defects are found in association with double-outlet right ventricle[195] and with transposition of the great arteries,[143] although again, the added complexity of the repair increases the risk. Hypoplasia of the left or right ventricle is an important risk factor and may contraindicate repair when the hypoplasia is pronounced.

Severe pulmonary vascular disease is a contraindication to corrective surgery and pulmonary artery banding in patients with atrioventricular canal defect, since mortality is high, and since prognosis is not improved even if the surgery is technically successful and recovery takes place. However, in infants and young children, particularly those below the age of 2 years, the diagnosis of pulmonary vascular obstructive disease should be made with caution, because a generalized increase in muscularity of the pulmonary arterioles can lead to increased pulmonary resistance measurements at catheterization. This increased muscularity may regress subsequent to successful surgery. Culpepper and colleagues[196] reported two patients with complete atrioventricular canal defects, aged 4 and 12 months, who had elevated pulmonary vascular resistances (1472 and 710 dynes·sec·cm^{-5}/m^2) preoperatively and who had a decrease in pulmonary resistance to the normal range at a postoperative cardiac catheterization. Evaluation of pulmonary resistance and blood flow in the presence of pulmonary vasodilators such as tolazoline, pulmonary wedge arteriography, and open lung biopsy may all be of assistance in evaluation for pulmonary vascular disease.

Prognosis

The long-term results of surgical therapy for these patients depend greatly on the degree of preoperative pulmonary vascular disease and on the extent of residual left atrioventricular valve regurgitation. In many instances, the left atrioventricular valve regurgitation is substantially reduced and the left-to-right shunt abolished or reduced to minimal levels by corrective surgery. The distal pulmonary vasculature can be effectively protected by pulmonary artery banding in most patients. However, when severe pulmonary vascular disease is present preoperatively, morbidity and mortality are high, and improvement may not occur even in patients who survive operation. Postoperative arrhythmias can occur, including complete heart block, and may increase in incidence as patients grow older. With advancing age, patients may also require mitral valve replacement.

Partial Atrioventricular Canal Defect

Immediate and long-term results following repair of partial atrioventricular canal defect were described in 35 patients by Stewart and colleagues.[197] Mean age at the time of operation was 8 years. Two operative deaths occurred. One death, in a patient 1.5 years of age with systemic pulmonary artery pressure before surgery, was secondary to ventricular fibrillation 48 hours after operation. A second death, in a patient 60 years of age, was secondary to unexplained low cardiac output without substantial mitral valve incompetence. Two patients required reoperation. One had closure

of a recurrent atrial septal defect 4 years after the initial operation. In a second patient progressive mitral valve incompetence developed over several years; this patient underwent mitral valve replacement. At the time of their last followup examinations, all surviving patients were in New York Heart Association functional class I. Heart size was normal on chest roentgenogram, and all were in normal sinus rhythm. Before operation 17 of the patients had either moderate or severe mitral valvular incompetence. After initial operation, only one patient had moderate or severe mitral valve incompetence.

The clinical course of 52 adult patients with partial atrioventricular canal defects seen between 1955 and 1981 were reviewed by Hynes and colleagues.[198] The mean age of the patients was 37 years and all patients were 20 years of age or older. Forty of the patients (77%) had either no symptoms or mild symptoms at the time of operation. Ten patients (19%) were in New York Heart Association class III and two patients (4%) were in New York Heart Association class IV preoperatively. All 18 patients aged 45 or older were symptomatic to some extent with palpitations, exertional dyspnea, and/or chronic fatigue. Nine patients were in chronic atrial fibrillation preoperatively and one patient had intermittent complete heart block and a pacemaker. Forty-seven of the patients underwent surgical repair. There were three operative deaths, two of which were secondary to acute respiratory distress in the immediate postoperative period, and one of which was secondary to refractory ventricular fibrillation 24 hours postoperatively. There were two late deaths, one in a patient who had severe congestive heart failure due to mitral valve insufficiency preoperatively, and one in a patient with severe postoperative hemolysis probably secondary to a mechanical mitral valve prosthesis. Postoperative atrial arrhythmias requiring treatment were present in 15 of the patients (34%).

The study by Somerville,[199] which examined the clinical course of 122 patients with ostium primum atrial septal defect seen during a 6-year period from 1958 through 1964, documented a substantial incidence of disabling symptoms and cardiac-related deaths in untreated patients with partial atrioventricular canal defects. The number of deaths and severe symptoms increased markedly with increasing age. Deaths occurred at all ages. The youngest age at death was 2 weeks and the oldest 56 years. Eight of 96 patients (8%) less than 30 years of age were severely disabled and five deaths were recorded in patients less than 30. Seven of 27 patients (27%) over 30 years of age were severely disabled and deaths were recorded in 7 patients over 30 during the course of the study. Arrhythmias were the most common cause of deterioration. Arrhythmias were uncommon before age 30 but thereafter steadily increased in incidence so that absence of arrhythmias was unusual in the sixth and seventh decades of life. Atrial fibrillation was a major cause of symptoms. The commencement of atrial fibrillation was noted to coincide with the onset of severe dyspnea, raised jugular venous pressure, increasing heart size, and hepatomegaly. Spontaneous complete heart block developed in six of the patients and was tolerated poorly. Severe mitral insufficiency was the most common cause of symptoms in patients in sinus rhythm. Pulmonary vascular disease occurred in only 5 of 122 patients (4%), and 2 deaths were attributed to pulmonary vascular disease. It is of interest that no patient who had deteriorated as the result of an arrhythmia had evidence of pulmonary vascular disease.

Considered together, the above clinical studies of patients with partial atrioventricular canal defects support the conclusion that successful corrective surgery is associated with an improved prognosis in patients with partial atrioventricular canal defect. The studies also support the conclusion that prognosis is better in patients with large shunts that are repaired before adulthood. Relief of the volume overload secondary to left-to-right shunting through the atrial septal defect should reduce the stimulus for atrial enlargement and the consequent propensity to develop atrial arrhythmias.

However, because reoperation for mitral valve replacement is sometimes necessary, the indications for surgery should be carefully evaluated in infants and young children in whom small size would make valve replacement technically difficult. Indications for surgery should also be carefully evaluated in asymptomatic patients with this disorder who do not have large left-to-right shunts. Patients with small left-to-right shunts and low pulmonary artery pressures are probably at relatively low risk for complications secondary to the partial atrioventricular canal defect. Substantial evidence is not available to suggest that surgery improves prognosis in these patients.

Complete Atrioventricular Canal Defect

Early reports of pulmonary artery banding in patients with atrioventricular canal defect suggested that a high operative mortality was associated with the procedure. Somerville and colleagues[200] reported four operative deaths and one late death in 12 patients with atrioventricular canal defects who underwent banding. Eleven of the patients were under 1 year of age and one patient was 2 years old. Other investigators described similar results. However, recent data suggest that advances in surgical technique and postoperative care have substantially lowered the mortality of pulmonary artery banding in infants with atrioventricular canal defect.

Silverman and colleagues[186] noted a 4.7% in-hospital mortality for pulmonary artery banding in 21 consecutive infants. Repeat cardiac catheterization, performed at a mean of 19.6 months after banding demonstrated an average peak systolic band gradient of 41 mm Hg. In one patient the pulmonary artery band migrated distally to occlude the left pulmonary artery. Two late deaths occurred 6 to 12 months after pulmonary artery banding, one from respiratory infection and one from unknown causes. Four patients from this series later underwent successful corrective surgery with debanding of the pulmonary artery. The authors concluded that pulmonary artery banding was a rational alternative for initial treatment of symptomatic infants with complete atrioventricular canal defects, particularly in the presence of anatomic variants such as single left ventricular papillary muscle, relative hypoplasia of either the left or right ventricles, or left ventricular outflow tract obstruction. Williams and colleagues[165] have developed an individualized management plan, based on their experience in a five-year study of 46 children with complete atrioventricular canal defects. They suggest banding of the pulmonary artery in infants less than 4 to 5 kg in weight. Corrective surgery is advocated in larger infants and children when not contraindicated by unusual anatomic features or pulmonary vascular disease. With this approach, Williams and colleagues reported one death in the immediate postoperative period and three deaths from 8 months to 2½ years postoperatively for a late survival rate of 91%. Thirty-two children had undergone successful corrective surgery at the time of the report.

Other investigators have demonstrated that complete atrioventricular canal defects can be repaired primarily in early infancy with a low mortality rate. Bender and colleagues[201] performed corrective surgery on 24 consecutive infants with complete atrioventricular canal defects. Operative mortality was 8% (2 of 24). Both operative deaths occurred in infants with associated anomalies—coarctation of the aorta in one case and total anomalous pulmonary venous connection in the other. One late death occurred, and one patient required a pacemaker postoperatively. Postoperative cardiac catheterization in seven surviving patients demonstrated an average drop in peak systolic pulmonary artery pressure to 27 mm Hg. Preoperative pulmonary artery peak systolic pressure was 81 mm Hg in the 21 patients.

The functional and anatomic characteristics of 310 consecutive patients undergoing repair of atrioventricular septal defects from 1967 to 1982 were reviewed by Studer and colleagues.[150] Age was not found to correlate with risk after 1976. However, severity of atrioventricular valve incompetence, functional status preoperatively, presence of major associated cardiac anomalies, presence of interventricular communication, and hypoplasia of the left or right ventricle were found to be major risk factors. Actuarial risk for corrective surgery was determined to be 0.6 to 4% for patients in New York Heart Association functional class III without an interventricular communication, depending on the degree of atrioventricular valve insufficiency and 5 to 13% for such patients with an interventricular communication. In this series, surgically induced complete heart block developed in five patients, for an overall incidence of 1.6%. Four of these five cases of heart block occurred either in patients with major associated anomalies in addition to atrioventricular canal or after atrioventricular valve replacement. Thus heart block occurred in only 1 of 231 patients (0.4%) without major associated anomalies who underwent routine repair of atrioventricular canal. Actuarial survival at 12½ years after surgery was calculated to be 95% when mild atrioventricular valve insufficiency was present and 88% in the presence of moderate to severe atrioventricular valve insufficiency. Late followup information was available on 258 patients who survived surgery. Nineteen of these patients died before hospital discharge. Two deaths were of noncardiac origin. Two deaths occurred in patients with severely elevated pulmonary vascular resistance. Ten deaths occurred in patients known to have failure of the left atrioventricular valve repair.

Clapp and colleagues recently reviewed the course of 121 patients with complete atrioventricular canal defects who were seen over 10 years.[202] Of these patients, 70 underwent corrective surgery. Perioperative mortality was 30% overall (21 of 70). When six patients with hypoplastic right or left ventricles, five patients with a double-orifice mitral valve or deficiency of mitral tissue, and five patients with pulmonary vascular obstructive disease were excluded from the group, perioperative mortality was 13%. Three of the 49 survivors of corrective surgery died 17 to 42 months postoperatively. Two deaths were attributed to heart failure and severe pulmonary artery vascular disease. One unexpected death occurred 17 months after surgery. One patient required a pacemaker. No progressive rhythm disturbances were noted.

The study of Neufeld and colleagues[157] suggests that advanced pulmonary vascular disease develops in patients with complete atrioventricular canal between 6 months and 1 year of age. Lung specimens were examined from open biopsy or autopsy specimens in 44 patients with complete atrioventricular canal defects. After 1 year of age, Heath–Edwards grade 3 and 4 histologic changes were present in most patients who had not undergone surgery, suggesting that irreversible pulmonary vascular disease had developed by this age. Biopsy specimens from infants less than 6 months of age often exhibited medial hypertrophy but did not show changes suggestive of irreversible disease.

The above studies support the conclusion that prognosis is improved by surgical intervention in patients with complete atrioventricular canal defects. However, at least palliative pulmonary artery banding must be performed within the first year and in many cases within the first six months of life in order to prevent the onset of irreversible pulmonary vascular disease. Clearly, individual patients with complete atrioventricular canal defects can be successfully treated either with primary intracardiac repair or with a staged approach involving pulmonary artery banding and subsequent corrective surgery. There are experienced advocates of both approaches.

Primary repair is attractive for many reasons. The period during which the ventricles are subject to volume and pressure overload is reduced by early primary repair. Hopefully this will translate into improved ventricular function after correction and a reduced incidence of ventricular fibrosis and dysfunction in later life. Even when patients have successful results from banding, they still are at risk for developing complications such as embolic phenomena and brain abscess while they await corrective surgery. Additionally, patients who undergo banding must still face the risk of corrective surgery, which may be increased by the need to take down the band.

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CHAPTER 61

Patent Ductus Arteriosus

Charles E Mullins

This chapter will cover the isolated persistent patent ductus arteriosus in the postneonatal infant, the child, and the adult, but will not deal with the patent ductus in the premature or early neonatal period. The ductus arteriosus is the only normal and essential structure in the fetus that becomes abnormal only by its persistent patency in the postfetal circulation.

EMBRYOLOGY

The ductus arteriosus embryologically originates from the distal portion of one of the sixth paired aortic arches[1] and provides a communication between the pulmonary artery and the descending aorta. The left, right, or both ductus can persist.[2,3] The persistence of either a left or right ductus and its course and connections from the aorta or its major branches to the pulmonary artery is closely associated with the development of the aortic arch. The ductus can connect from either the proximal right or left pulmonary artery to virtually any location on the aortic arch or proximal portions of any of the brachiocephalic vessels. The variations in the connections and the course of the ductus are related to where the lateralization ''breaks'' occur in the embryonic double aortic arch and the relation of the ''break position'' to the aortic end of the embryonic sixth arches (Fig. 61–1).

In the infant with a normal left aortic arch, the ductus originates from the distal left sixth arch and connects the main pulmonary artery to the left descending aorta distal to the origin of the left subclavian artery (position 4, Fig. 61–1). With a right aortic arch, a persistent ductus still usually will arise from the distal *left* sixth arch along with a remnant of left dorsal aorta (the Kommerell's diverticulum) either as an isolated structure off of the right descending aorta or in conjunction with an anomalous left subclavian artery (position 4, Fig. 61–1). In both situations the ductus or its ligamentum will pass behind the trachea and esophagus and create a vascular ring.[4] Rarely with a right aortic arch, the ductus will arise from the original distal right sixth arch and connect the proximal right pulmonary artery to the right descending aorta just distal to the origin of the right subclavian artery (position 1, Fig. 61–1). With ''breaks'' in the embryonic double arch at different locations the rare anterior ductus off of the base of a carotid or innominate artery or even the ductus arising from an isolated subclavian artery will occur. Bilateral ductus is created by the persistence of both distal sixth arches connecting the pulmonary arteries to various portions of the aortic arch or brachiocephalic vessels.

INCIDENCE

A persistent patent ductus arteriosus, as an isolated lesion, has been estimated to occur in between 1 in 2,500 and 1 in 5,000 live births.[5–7] As an isolated lesion, it represents between 9 and 12% of all presenting congenital heart lesions. In most series, there is a sex difference with a 2:1 female-to-male ratio.[8]

The ductus arteriosus may coexist with virtually all other congenital heart lesions and should be considered when the clinical features of left-to-right shunting seem out of proportion to the particular lesion being considered. The persistent ductus definitely should be ruled out when a patient with a more complex lesion is being considered for cardiopulmonary bypass. There are complex cardiac lesions where the persistence of the ductus is critical for

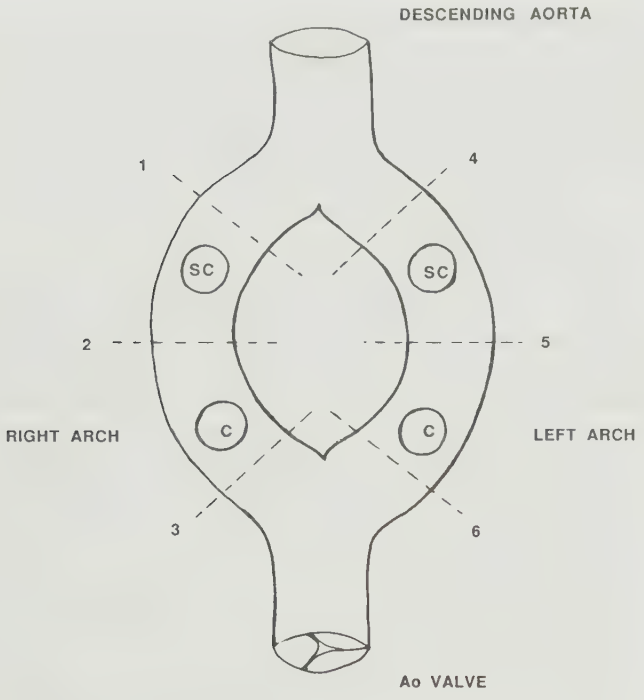

Fig. 61–1. Schematic diagram of the embryonic double aortic arch system. The potential positions or sites for "breaks" or divisions of a double arch in the eventual formation of a single right or left arch are numbered 1 through 6. The origin of the carotid and subclavian arteries on the embryonic double aortic arch are indicated by "C" and "SC" respectively. The usual left aortic arch with normal brachiocephalic vessels "break" at position 1 and the usual left ductus inserts near position 4.

the survival of the patient—the so-called ductus-dependent lesions. These lesions will be discussed later.

HISTOLOGY—MECHANISM OF NORMAL CLOSURE

The walls of the ductus arteriosus are similar in overall thickness to the adjacent pulmonary artery and aorta, and do contain an intima, media, and adventitia. However, in contrast to the true arterial structures where the media of the arteries is made up primarily of circumferential elastic fibers, the medial layer of the ductus arteriosus is composed of smooth muscle—longitudinally orientated in the inner layers and in a predominantly circular arrangement in the outer layers.[9–11] These layers of smooth muscle contain concentrically arranged loose laminae of elastic tissue and a network of very tiny, thin-walled vessels.[12,13] The intimal layer of the ductus wall is irregularly thickened into so-called "mounds" and contains considerable mucoid material.[14,15]

In the fetus, there is an environment of relatively low oxygen tension and a high level of circulating prostaglandins, both of which act to keep the ductus open.[16,17] The high levels of prostaglandins in the fetus are a result of minimal fetal circulation through the lungs where the prostaglandins are metabolized and of high levels of prostaglandin production in the placenta.[18] With birth, the placenta is removed from the circulation and the lungs are expanded, thus removing the major source of prostaglandins while at the same time, activating the organ where most of the prostaglandins are metabolized. Along with this, the normal respirations of the infant markedly increase the oxygen tension in the blood. The combined effect of the increased oxygen and decreased prostaglandins results in a contraction of both the longitudinal and circular smooth muscles within the ductal walls.[17,19] This, in turn, shortens the ductus and thickens the walls effectively obliterating the lumen.[17] The typical shape of the ductus has fostered the idea that the obliteration process begins at the pulmonary end, however, there is no evidence for this obliteration occurring preferentially at any location along the ductus. The aortic end of the ductus is probably held open by the combination of higher aortic pressure and, in turn, more rigid adjacent aortic wall. The functional obliteration of the ductus usually occurs within the first 15 hours after delivery. Later on, after this functional obliteration, there is enfolding of the endothelium with disruption of the intimal layers and subintimal necrosis.[20] This leads to later fibrosis and scarring with a permanent seal of the ductus.

ETIOLOGY—CAUSE OF PATENCY

All of the factors responsible for continued patency of the ductus are not known and even those shown to have an effect on ductus patency are not totally understood.

Prematurity and Hypoxemia

Certainly significant prematurity or immaturity of the infant at the time of delivery contributes to abnormal patency of the ductus.[21] Whether this is due to a paucity of the normal constricting muscles within the ductus or whether it is due to an absence of the metabolites in the immature lungs that normally clear the prostaglandins is not fully understood.[22] Causes of persistent low oxygen tension in the blood such as significant respiratory problems in the neonate[8,21,23–25] or an environment with lower oxygen tension such as very high altitudes[26–28] will contribute to persistent patency of the ductus.

Infectious, Genetic, and Environmental Factors

A rubella infection in the first trimester of pregnancy, particularly in the first 4 weeks of gestation, has a very high association with persistent patency of the ductus arteriosus.[29,30] The incidence of a persistent ductus in those rubella-affected infants, including those in association with other cardiac defects, has been as high as 85%. As an isolated cardiac lesion, it appears to occur in 50% of infants definitely affected with rubella.[31,32]

There also appears to be a genetic factor. Siblings of patients with a patent ductus have as high as a 2 to 4% incidence of recurrence of the same lesion.[33,34] The mechanism of genetic inheritance has not yet been determined and, in fact, may well be an additional environmental rather than genetic factor. In the ongoing Texas Children's Hospital study group of ductus arteriosus, it appears that there is a nonracially related, socioeconomic relationship to patency of the ductus with a higher incidence of patients with a patent ductus from a lower socioeconomic status than patients with any other lesion.

Even when an etiologic agent is implicated in causing patent ductus arteriosus, the mechanism of this etiology has not been worked out. Most cases of patent ductus arteriosus still seem to be random.

ANATOMY

In the usual heart with a normal left aortic arch, the persistent ductus forms a communication from the pulmonary artery just at the junction of the main and left pulmonary arteries, to the descending aorta just distal to the origin of the left subclavian artery. In doing so it takes a slight cephalad-to-caudal course as it passes from the more anterior pulmonary artery to the posterior descending aorta (Fig. 61–2). The ductus arteriosus may persist in an infinite variety of shapes and sizes. The "classic" or typical persistent ductus has a conical shape with a large aortic end tapering toward the pulmonary artery with the narrowest area of the ductus close to the junction with the pulmonary artery (Fig. 61–2). The "cone" may be short and broad or long and narrow, and it can be symmetrical or totally asymmetrical (Fig. 61–3). The ductus also can have a long tubular, or fingerlike, shape that can be straight or very tortuous in its course (Fig. 61–3). The total length of the persistent ductus, regardless of its shape or diameter, may vary from millimeters to centimeters. The base of the aortic end of the ductus can vary in size from several millimeters to several centimeters, again independent of the shape or the length of the ductus. The so-called "window ductus," seen externally as having no length, is a very short, large ductus with a large aortic base (Fig. 61–3). The ductus may occur with a right aortic arch (Fig. 61–4); rarely two ducti appear in the same patient (Fig. 61–5).

In congenital cardiac defects with very severe pulmonary stenosis or pulmonary atresia (the so-called ductus-dependent lesions where there is little or no prograde flow possible through the pulmonary valve during fetal or neonatal life), the ductus tends to be smaller and more tortuous. It usually arises more cephalad on the aortic arch with its aortic origin positioned more toward the concave apex of the arch (see Fig. 61–6), presumably due to the fetal blood flow in these ductus being from the aorta to the pulmonary artery. These ductus have the same histologic anatomy and tendency to close after delivery of the infant as the more typical or usual ductus.

The variations in anatomy of the persistent ductus account for many of the differences in physiology and presentation of patients with persistent ductus arteriosus.

PHYSIOLOGY

In the normal fetal circulation the nonaerated and unexpanded lung beds receive only 5 to 8% of the blood entering the pulmonary artery with the fetal ductus arteriosus serving as the predominate route of circulation for the blood passing through the fetal right ventricle and main pulmonary artery.[35] In this capacity 55 to 60% of the systemic circulation to the fetus passes right to left through the ductus. As a result, the fetal ductus normally is a large structure equal in diameter to the main pulmonary artery and descending aorta. Normally with the first few breaths by the neonate, the lungs expand, instantaneously expanding the pulmonary vascular bed and beginning the lowering of the pulmonary vascular resistance. Along with this the ductus begins to constrict and there is an immediate shift in the flow of the right ventricular/pulmonary artery blood away from the ductus arteriosus and into the lungs. Normally the constriction of the ductus continues rapidly and functionally is completed by 10 to 18 hours after birth. Until the functional closure is completed and as soon as the pulmonary resistance is lower than systemic, there will be some left-to-right flow from the aorta, through the ductus and into the pulmonary arteries. Structural closure is usually completed by the fifteenth to twenty-first day of life. Only when the ductus remains patent after 3 months is it considered abnormal.[36]

With patency of the ductus and once the pulmonary vascular resistance has dropped below the systemic vascular resistance, blood will flow from the aorta into the pulmonary artery resulting in a net left-to-right shunt. In the presence of normal pulmonary resistance, the left-to-right flow through the ductus continues throughout systole and diastole. In the normal postnatal circulation the fully saturated aortic blood passes from the descending aorta through the ductus and mixes with the systemic venous blood from the right ventricle in the pulmonary artery. This combination of blood passes through the lungs, into the left atrium, into the left ventricle, and back into the aorta. This results in an increased volume load on the left atrium and left ventricle. The resultant increase in left ventricle stroke volume is proportionate to the size of the left-to-right shunt. Unless the volume load is massive and results in significant elevation of pulmonary artery pressure, there

Fig. 61–2. Typical patent ductus arteriosus. Posteroanterior (left) and lateral (right) aortograms with injection into the descending aorta just distal to the ductus. Typical catheter passage from the femoral vein, through the right heart into the pulmonary artery and through the ductus into the descending aorta.

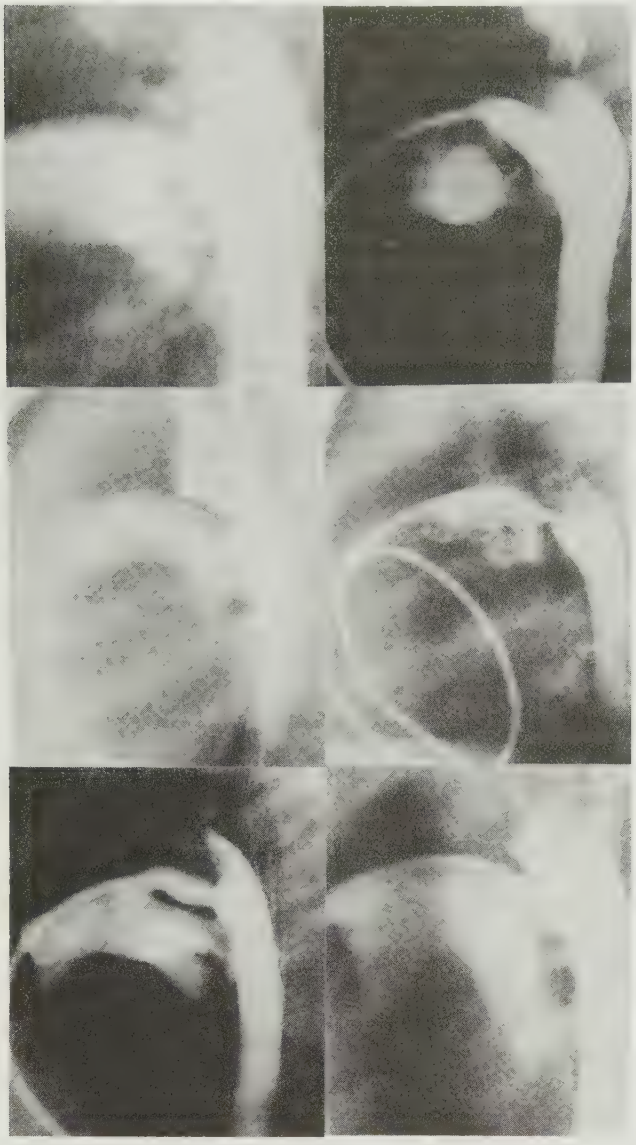

Fig. 61–3. Variations in the size and shape of the persistent ductus. Comparable lateral angiocardiograms with injection into the descending aorta. Short broad-based ductus (upper left); large, long conical ductus (upper right); small symmetrical conical ductus (middle left); small asymmetrical conical ductus (middle right); long tubular ductus (lower left); and a very short large "window" ductus.

is no added volume work and little or no pressure work on the right ventricle. As a result of the increased left-sided flow, there is distention and dilation of the left atrium and left ventricle. The left ventricle hypertrophies to adjust to the added work load.

With the increased left ventricle stroke volume and the central runoff from the aorta into the pulmonary artery, which continues throughout diastole, there is a resultant wide pulse pressure generated in the aorta. This increase in pulse pressure is proportionate to the volume of flow through the ductus.

Volume Changes

In the presence of a patent ductus arteriosus there is an absolute increase in the total circulating volume of the patient proportionate to the amount of left-to-right shunt. The net increase in volume is trapped or recirculating in the lungs while the circulating systemic volume remains normal or only slightly decreased. This results in pulmonary engorgement and decreased overall pulmonary compliance, again, proportionate to the amount of shunting. This pulmonary overcirculation causes most of the symptoms of a patent ductus. The reaction of the pulmonary vascular bed to the increased flow is totally unpredictable. Usually with a very large flow there will be some increase in the pulmonary vascular resistance, thus preventing massive overcirculation. However, there are individual patient variations in response to this increased pulmonary flow.

Nature of Left-to-Right Shunt

The amount of flow through the ductus varies with the size and shape of the ductus and with the differences between the systemic and pulmonary resistances.

Ductus Size

When the ductus remains widely patent, the only impediment to pulmonary flow from the aorta is the total pulmonary resistance. In the neonate with a large ductus arteriosus, the fetal pulmonary vascular resistance usually drops more slowly, allowing a more gradual but progressive increase in pulmonary flow. The increased pulmonary flow will continue to increase until the *total* pulmonary resistance increases and eventually reaches systemic levels as a result of both the reactivity of the pulmonary arterioles and the

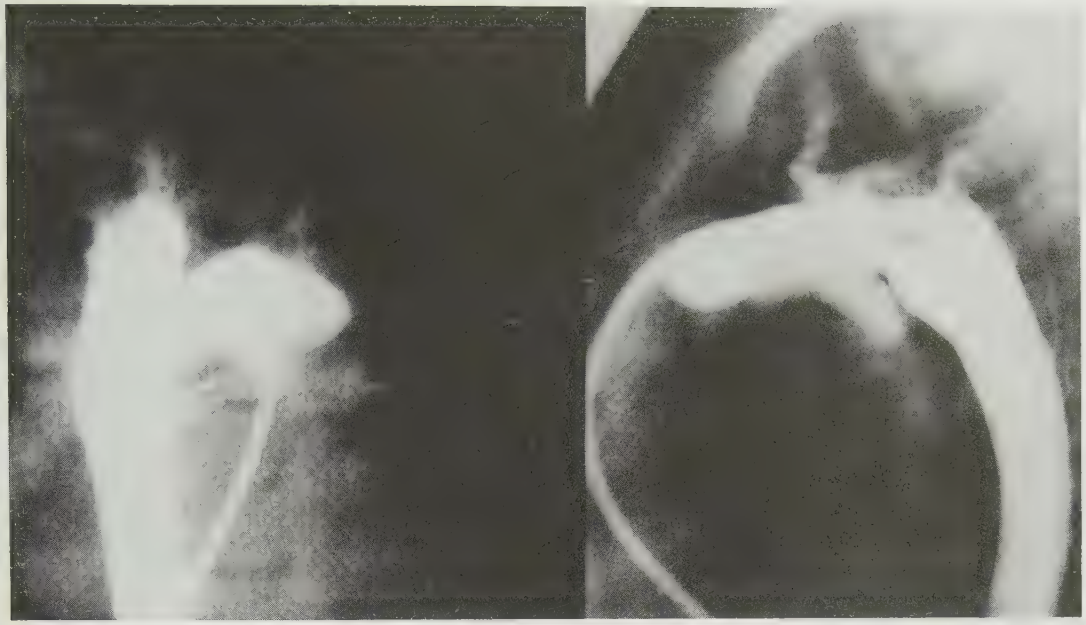

Fig. 61–4. Right ductus arteriosus. Posteroanterior (left) and lateral (right) descending aorta angiocardiogram shows ductus off right descending aorta. Catheter passage is from femoral vein through right heart, pulmonary artery, ductus into the descending aorta.

elevation of the left ventricular end-diastolic and left atrial pressures and/or the patient goes into florid pulmonary edema and heart failure.

The smaller the narrowest portion of the ductus, the less the flow through the ductus. In the absence of the other variables, the flow through the ductus and the net left-to-right shunt will be proportionate to the size of the narrowest area of the ductus.

Ductus Shape

The shape and, in turn, course of the ductus may vary the total flow and the velocity of flow through the ductus particularly in the case of the long and tortuous ductus. In this particular type of persistent ductus, the additional length of the ductus can add to the resistance to flow. Transient changes in shape and tortuosity of the ductus with slight changes in relative positions of adjacent mediastinal structures can instantaneously change flow through the ductus accounting for variations in clinical findings from minute to minute. This type of anatomy accounts for the "intermittent ductus." Marked alterations in the size and shape of the ductus can occur during cardiac catheter manipulations in the ductus even in patients well past the newborn period (Fig. 61–7).

Systemic Pressures

The higher the systemic pressure, the higher the driving pressure through the ductus and vice versa for lower systemic pressures. Thus abnormalities that increase systemic pressure will increase the ductal flow and increase any symptoms due to the ductus. This is particularly true of generalized systemic hypertension or localized upper extremity hypertension proximal to the aortic origin of the ductus as is the case in the usual coarctation of the aorta. On the other hand, other large intracardiac shunts or left ventricular outflow obstructive lesions that decrease systemic pressure, may decrease the magnitude of ductal shunting.

Pulmonary Resistance

The total pulmonary resistance is the major variable in the determination of the flow through the ductus. This is particularly so in the large, wide-open ductus that approaches the diameter of the

Fig. 61–5. Bilateral ductus arteriosus. Posteroanterior cineangiocardiogram of a catheter passage through a left ductus with injection into the left descending aorta (left frame). A large retroesophageal right subclavian artery fills from this injection. A lateral recirculation frame of the same injection (right frame) shows the catheter still through the left ductus with a right ductus filling an isolated right carotid artery and emptying into the stenotic right pulmonary artery.

Fig. 61–6. Large vertical ductus. A lateral aortogram in a patient with transposition of the great arteries and pulmonary atresia showing the origin of the ductus from the underside of the transverse arch.

adjacent aorta, but can be a significant variable in a ductus of any size. The total pulmonary resistance is a sum of the actual pulmonary vascular resistance plus the total outflow resistance from the pulmonary vascular bed. A high total pulmonary resistance, regardless of cause, can markedly decrease or even reverse flow through the ductus and will decrease the usual signs and symptoms of the persistent ductus. In the otherwise normal heart, the pulmonary resistance increase is usually in the pulmonary vasculature itself. Associated lesions such as mitral stenosis or various types of obstruction to pulmonary venous return can elevate the total pulmonary resistance to the point of stopping or even reversing ductal flow in the presence of normal pulmonary vascular resistance.

Reversed Ductus

A reversed ductus refers to the situation where there is right-to-left flow from the pulmonary artery to the aorta through the persistent ductus. This is a result of marked elevation of total pulmonary resistance plus or minus associated decreased resistance on the aortic side of the ductus. In the otherwise normal circulation, this will result in desaturated blood passing into the descending aorta from the pulmonary artery with resultant lower body (differential) cyanosis. This occurs most often with severe pulmonary vascular obstructive disease but also in the presence of left heart inflow obstructive lesions such as obstructed pulmonary venous connection, cor triatriatum, or mitral stenosis.

In the newborn with transposition of the great arteries and no other source of mixing, there will be bidirectional shunting of blood through the ductus. The unsaturated aortic blood will shunt from the aorta into the pulmonary circulation. However, with no other defect to allow mixing, or in this case, venting of the pulmonary bed, the lungs become "full" with resultant massive overcirculation and/or reactive increase in pulmonary resistance or both. The resultant total pulmonary resistance reaches systemic levels and a reversal of flow (pulmonary to aortic flow) results. Once the lungs are "full," this right-to-left and left-to-right flow occurs instantaneously and almost simultaneously within each cardiac cycle. In the rare combination of transposition of the great arteries, patent ductus, and coarctation of the aorta (pre- or juxtaductal), this will create the pathopneumonic situation of allowing desaturated blood to perfuse the upper body from the right ventricle and saturated blood from the left ventricle and pulmonary artery to perfuse the lower body. In these patients there will be bidirectional shunting at the ductus, however, the saturated blood of the right-to-left shunting will be directed predominately to the lower half of the body by the coarctation.

CLINICAL FEATURES OF THE PERSISTENT PATENT DUCTUS

Medical History

There is no characteristic clinical history for the patient with a persistent patent ductus. The presenting symptoms depend primarily on the anatomic and physiologic features of the ductus in each individual. The majority of patients will present with a heart murmur heard on routine physical examination and deny any symptoms related to the heart. A few patients will present with signs of decreased exercise tolerance or pulmonary congestion in conjunction with a murmur. These presentations can occur at any age. At the other extreme there is the infant with the large persistent ductus who presents at 3 to 6 weeks of age with tachypnea, diaphoresis, inability to feed, and either no weight gain or even weight loss.

Physical Examination

There are typical or "classical" physical findings of the persistent patent ductus arteriosus that are almost diagnostic of the ductus. The typical patient usually appears well with normal respirations and heart rate. The blood pressure usually shows a widened pulse pressure. On inspection there usually will be prominent or even visible suprasternal and carotid arterial pulsations.

The hallmark of the persistent patent ductus is the continuous or "machinery" murmur.[37] This murmur begins shortly after the first heart sound, crescendos to a maximum at about the second sound, and decrescendos throughout diastole. In intensity it is usually grade three, four, or five over six and maximum in the first and second left intercostal spaces at the left sternal border. It may be localized to that area or radiate widely to the suprasternal notch as well as down the left sternal border and out over both lung fields. As the examiner tracks down the sternum, the diastolic component becomes less apparent and the murmur sound only systolic. This is particularly true in the small infant.

The continuous murmur is usually associated with several other characteristic clinical signs. The grade four and louder murmurs

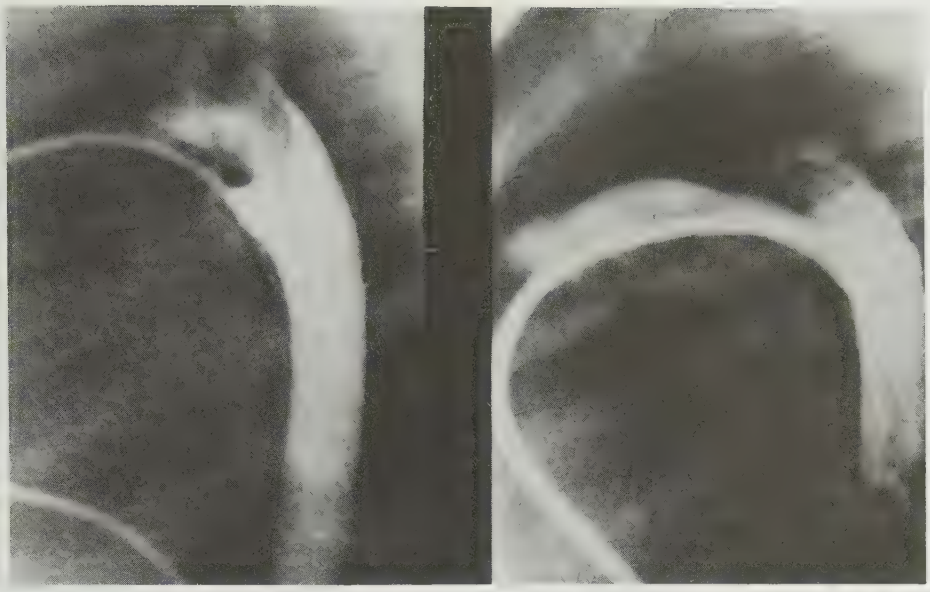

Fig. 61–7. Variable ductus. Lateral angiocardiograms obtained during the same catheterization in a 16-month-old infant. A 6 French catheter virtually occludes a "typical" small conical ductus (left frame). An 8 French sheath passing through the same ductus (right frame) allows free passage of contrast through a now large long tubular ductus approximately 10 minutes after the first angiocardiogram.

will be associated with a continuous thrill with the same localization as the murmur. There is often a left ventricular lift or heave to palpation. The second heart sound is increased in intensity, widely but variably split, and has a characteristic "slapping sail" sound. In the patients with a larger ductal flow there will be a diastolic flow rumble at the apex. The peripheral pulses will be prominent and bounding and with the larger ductus in the thinner patients, even visible in the axillary and femoral areas.

All of these clinical features may be altered in each individual patient according to the differences in the size, anatomy, and physiology of the ductus but usually the clinical findings are characteristic enough to make the diagnosis.

Variables

The variables in the ductus that alter the clinical findings are, of course, all interacting and usually cannot be separated; however, they do have some distinguishing features when they occur as isolated variations.

Ductus Size and Shape

The typical persistent ductus has a medium- to high-pitched, rough, continuous murmur that peaks at the second sound and extends throughout diastole. The smaller the ductus, usually the higher the pitch and the more localized is the continuous murmur. At the same time, the other clinical signs are less prominent with these very small ductus. The murmur in the small tortuous ductus actually may change its qualities from minute to minute with changes in body position, even to the point of disappearing completely. The larger ductus, on the other hand, usually has a louder, lower frequency, and rougher sounding murmur that ends before the end of diastole. Unless there is associated increased pulmonary vascular resistance, the larger the ductus is, the more prominent are the associated signs.

Pulmonary Pressures (Resistance)

The higher the pulmonary resistance, the less overall flow through the ductus. In particular, the diastolic run-off is initially decreased and, in turn, the clinical signs are diminished proportionately. The alterations in clinical findings due to changes in pulmonary resistance will usually overshadow the effect of all of the other variables on the clinical features of the ductus. Elevated pulmonary resistance will decrease or eliminate first the diastolic component of the murmur and if the pulmonary resistance is high enough, even the systolic component of the murmur. The pulse pressure will decrease and with the elevation of right ventricular pressure and prolongation of right ventricular ejection time, the second sound will become louder and single.

Elevation of the pulmonary resistance above systemic resistance produces right-to-left shunting at the ductus with resultant blueness of only, or predominantly, the lower half of the body. This classical differential cyanosis is pathognomonic of a persistent ductus with right-to-left shunting.

Patient Age

The age of the patient alone does not necessarily alter the clinical findings of the ductus; however, at the extremes there are some common exceptions.

Premature and Newborn. In the usual normal newborn there is a gradual enough drop in pulmonary resistance so that abnormal flow into the pulmonary arteries is usually not detectable by auscultation for several weeks or more. With an extremely large ductus, particularly in the small newborn, the abnormal flow may be present only in systole so the infant may have only a benign-sounding systolic murmur and even one localized more down the left sternal border. However, the infant will have very bounding and often even visible peripheral pulses.

Older Adult. As a result of changes in pulmonary compliance with the changes of aging, emphysema, and at least some degree of elevated pulmonary vascular resistance, the diastolic run-off into the pulmonary circulation is usually lessened and, as a result, the classical murmur of the ductus may be altered so that only the systolic component persists. On the other hand, as the systemic vasculature generally becomes more atherosclerotic, the blood pressure as well as the pulse pressure usually increases, giving the impression of an even greater run-off.

Roentgenography

The x-ray findings will vary with the size of the ductus and the amount of left-to-right shunting. With the very small, yet noisy patent ductus, often there is a perfectly normal roentgenogram. The earliest x-ray finding is usually a prominent main pulmonary artery segment blending with a prominent aortic knob along the upper left heart border. With a moderate-sized persistent ductus, the heart shadow will be slightly enlarged with a downward displacement of the apex (left ventricular configuration) and the pulmonary vascular markings will be increased. There may be a noticeable double density of an enlarged left atrium. The larger the shunting through the ductus, the more prominent these x-ray features become.

Electrocardiography

The ECG in the small persistent ductus is usually normal by strict criteria. The ductus with a moderate or larger left-to-right shunt will show left ventricular hypertrophy and occasionally left atrial enlargement.

Echo and Doppler Cardiography

The aortic end of the ductus can be reliably visualized and often traced to the pulmonary artery by meticulously performed two-dimensional echocardiography procedures performed with that goal in mind. On the other hand, the marked variation in the size, shape, and course of the persistent ductus make it difficult to consistently and reliably visualize it in its entirety and, in turn, to describe accurately its shape or measure the diameter of its narrowest segment.

By careful exploration of the entire area around the usual site of entry of a ductus into the pulmonary artery, the continuous-wave Doppler can pick up infinitesimally small jets of abnormal flow in the pulmonary artery even in the face of otherwise large volume pulmonary flow. By this technique even the smallest, nonaudible persistent ductus can be detected, but again, usually only with meticulous technique and when the persistent patency of the ductus is specifically being looked for. With color-flow Doppler, the actual jet of abnormal flow through the ductus can be visualized and more information obtained about the size and shape of the ductus (Fig. 61–8).

The greatest value of echocardiograms/Doppler cardiograms in the diagnosis of the persistent ductus is to exclude other significant intracardiac lesions when there are typical signs of the ductus or in the converse situation, to suggest or identify the presence of a ductus in the presence of other major known intracardiac defects or when there are complications of the ductus that alter the typical or presenting signs.

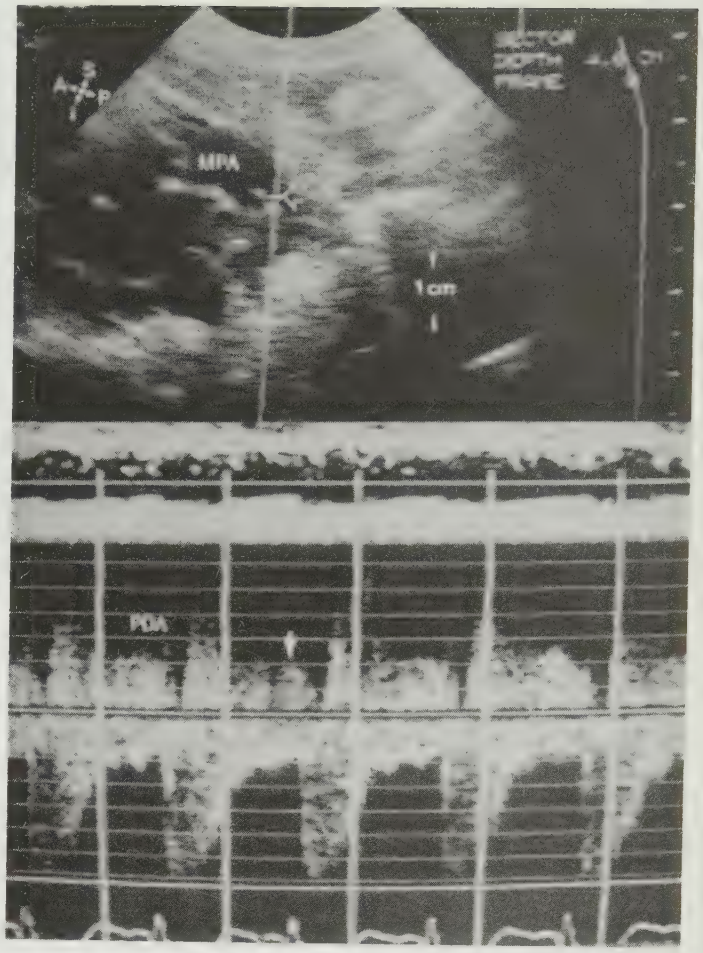

Fig. 61–8. Echocardiogram from a patient with patent ductus arteriosus, obtained from the suprasternal approach. Upper panel: the Doppler sample volume is in the ductus arteriosus (open arrow). A = anterior; S = superior; P = posterior; I = inferior. Lower panel: the Doppler tracing indicates the presence of continuous turbulent flow through the ductus into the pulmonary artery. MPA = main pulmonary artery, PDA = patent ductus arteriosus.

COMPLICATIONS OF PATENT DUCTUS

Patent ductus usually presents as an incidental finding with typical clinical findings unless there are complicating features. Most of the exceptions to this typical presentation occur in either the small infant or the older adult. The actual complications of the persistent ductus or the attempts to avoid these complications provide the major indications for surgical or other corrective procedures for the persistent ductus arteriosus.

Congestive Heart Failure

Congestive heart failure usually occurs in the very young infant with the large patent ductus or in the elderly with a large ductus after the effects of the chronic volume workload have taken their toll on the left atrium and left ventricle. In the elderly, the heart failure is often associated with atrial flutter or fibrillation. The failure is initially "left heart" with pulmonary congestion. Because of the large volume load and increased pressure in the pulmonary circulation, the right heart eventually must perform some of the extra work and, in the very large ductus, will also show signs of failure with hepatomegaly and even peripheral edema in the elderly or young infant. In the younger patients and many of the elderly, the congestive failure is reversible with the correction of the patent ductus.

Endocarditis

Bacterial endocarditis complicating a patent ductus is now an extremely rare occurrence.[38] Prior to the days of surgical repair and of routinely used antibiotics, endocarditis was one of the leading causes of death in adults with patent ductus arteriosus.[39,40] Both modalities of therapy became available at about the same time and with them a very marked decrease in this complication. Currently, even with antibiotic prophylaxis, an occasional case of

endocarditis will still be seen. This fact, plus the reported earlier high incidence and the ongoing need for prophylactic antibiotics, makes the prevention of endocarditis the major indication for correction of even the small ductus. The uncorrected patent ductus should be treated with the same vigorous antibiotic prophylaxis for the prevention of endocarditis as any other structural congenital heart lesion until it is corrected and for at least a year after the ductus has been completely corrected.

In the event that endocarditis should occur, most of the vegetations seem to accumulate at the pulmonary end of the ductus and shower emboli to the lungs, thus simulating a pneumonic or other pulmonary process. When endocarditis does occur on the patent ductus, it is recommended that it should be treated with a full course of the appropriate antibiotics determined from blood cultures before considering any surgical intervention. Surgical correction, in fact, should not be considered until several months after the completion of successful therapy and the tissues have had time to completely heal.

Aneurysm of Ductus

This extremely rare complication of the patent ductus usually occurs in the very young infant,[41] the very elderly patient,[42] or following surgery for the ductus[43,44] or endocarditis of the ductus. Spontaneously occurring aneurysms usually present as mediastinal masses with symptoms arising from the compression of adjacent nerves or pulmonary structures.[45] The diagnosis and exact details of aneurysms are best established by a quality angiocardiogram. When diagnosed, and when not due to an ongoing infection, the aneurysm should be removed surgically utilizing cardiopulmonary bypass and/or hypothermia with circulatory arrest. In the case of an infected aneurysm, the infection first should be treated completely unless there is unequivocal evidence for progression or expansion of the aneurysm in spite of the antibiotic therapy.

Pulmonary Vascular Disease

Most cases of pulmonary vascular disease associated with a patent ductus represent a concurrent condition present since birth and are usually not a result of the ductus. However, this is not always or at least not completely the case.[46,47] There are definitely documented cases of isolated patent ductus in adults with classical clinical signs of a ductus with a large left-to-right shunt and less than systemic pulmonary pressures and resistance that progresses on into unequivocal high pulmonary resistance and right-to-left shunting at the ductus. These cases are extremely rare; however, the difference between these patients and the majority that do not do this is not known, thus this potential complication represents another indication for the correction of all patent ductus.

DEFINITIVE DIAGNOSIS BY CARDIAC CATHETERIZATION

Catheter Passage

The usual patent ductus arteriosus can be diagnosed from the physical examination, x-ray and electrocardiogram studies, and when in doubt, usually confirmed with a carefully performed echo/Doppler evaluation. When there are atypical features, and particularly when precise echocardiographic studies by skilled echocardiographers are not available, then the definitive diagnosis must be by cardiac catheterization. With most cases of patent ductus arteriosus, in the performance of a right heart catheterization, as the catheter is manipulated from the right ventricle into the pulmonary artery, the catheter will selectively pass from the pulmonary through the ductus into the descending aorta. The catheter characteristically passes slightly laterally as the tip moves cephalad in the body and then courses slightly medially as the tip passes through the ductus and into the descending aorta and toward the patient's feet. This is not always the course of the catheter nor is it the only course that it may take through the ductus, so the catheter course alone should not be utilized to confirm or rule out the presence of a ductus. The passage of a catheter through a ventricular septal defect and around the arch or even through an aortic pulmonary window and subsequently around the arch, can be very similar. If the catheter passage through the ductus is accomplished, to confirm the presence of a ductus, it must be accompanied by an angiocardiogram.

Oxygen/Pressure Data

During the right heart catheterization there will be an increase in the measured oxygen saturation or content in the main pulmonary artery. Some increase in oxygen values continues out into both the right and left pulmonary arteries. In the usual ductus, the highest saturation is obtained in the main pulmonary artery adjacent to the orifice of the ductus with slightly decreased saturations in the branch pulmonary arteries. The amount of net increase in saturation will be dependent upon the size of the left-to right shunting and may be utilized to calculate the exact shunt. The average saturation from the distal pulmonary arteries should be used for the calculations rather than the saturation from the main pulmonary artery. Some pulmonary valve insufficiency is encountered with many ductus cases, particularly the large ones. This will result in an increase in oxygen saturation in the high right ventricular outflow tract as well as in the pulmonary arteries, and from the oxygen data alone, may cause confusion in the diagnoses with a ventricular septal defect. With the typical ductus, the pressures in the pulmonary artery are usually normal or very slightly elevated. With the large ductus, the pressures will be elevated in the right ventricle and pulmonary arteries, but rarely to, or near to, the systemic levels. When, with a patent ductus arteriosus, very high pressures at or near systemic levels do occur in the pulmonary artery, one must be suspicious of associated high total pulmonary resistance either on the basis of pulmonary vascular disease, pulmonary venous obstructive, or left heart inflow obstructive lesions.

Selective Angiography

The most definitive tool for the diagnosis and precise definition of the size and shape of a ductus is by means of a selective angiocardiogram. The preferred location for the injection of the contrast is into the descending aorta just distal to the aortic end of the suspected ductus. An injection of 1 ml of contrast per kilogram of patient body weight delivered within one or one and one-half heart beats in this location will clearly demonstrate the exact anatomy of the ductus (see Fig. 61–2). By injection in this location and with the predominate flow into the ductus occurring during diastole, the contrast will flow retrograde back into the mouth of the ductus and yet will not be diluted significantly by flow into the vessels of the head and neck, as is the case with

more proximal, particularly ascending aortal injections. The easiest and quickest technique for the performance of this angiocardiogram is to pass an angiocardiographic catheter prograde through the right heart and through the ductus into this position. The same location may be achieved be a retrograde catheterization. The best technique of filming is on cineangiocardiograms at a minimum of 30 and preferably 60 frames per second. The best view for the usual ductus is a straight lateral projection. Occasionally, a long tortuous ductus will take a peculiar course that will be better elongated by some angulation determined from the lateral view.

DIFFERENTIAL DIAGNOSIS

The classical persistent ductus arteriosus should be diagnosed by the skilled pediatric cardiologist from the typical physical examination, roentgenograms, and ECG. Many other lesions can produce a continuous murmur, however, when meticulous attention is given to the precise characteristics of the murmur plus the basic laboratory tests, the diagnosis of the ductus should be established. Or, on the other hand, some other lesion immediately should be suggested. Difficulty in the differential diagnoses of the persistent patent ductus arteriosus should only arise with the atypical or complicated patent ductus. Most of the lesions that can mimic or be confused with the patent ductus are included in the list of the differential diagnosis.

Ventricular Septal Defect in Infancy

The large persistent ductus in the young infant with congestive heart failure may sound more like a ventricular septal defect with only a long pansystolic murmur being easily audible. With the patent ductus, by very careful auscultation, some spillover of the murmur into diastole will be audible and the loud slapping second sound will be present. Unless the heart failure is profound, the peripheral pulses with the ductus will be bounding and should alert one to consider a patent ductus and pursue this with an echocardiogram and/or catheterization.

Aortic Pulmonary Window

The lesion that can mimic the patent ductus most closely and the one that is the most difficult to differentiate clinically is the rare aortic pulmonary window, also known as an aorticopulmonary fenestration. With this defect there is incomplete division of the embryonic common truncus resulting in a communication between the ascending aorta and the main pulmonary artery yet the development of two semilunar valves. The net physiologic effect can be exactly the same as the persistent ductus and, like the ductus, depends on the same variables of size of the defect and relative pulmonary and systemic resistances. The aortic pulmonary window usually is a very large defect and, as a consequence, results in a very large pulmonary flow. Since the communication with the pulmonary artery is proximal to all of the branches of the aorta and is so large, the net effect is that most of the left ventricular output is ejected almost directly into the pulmonary artery, with the "left over" flow continuing on to the systemic circulation. The result is that there actually is a decreased flow to the body so that the pulses may not feel full and the pulse pressure may not be increased. The murmur usually is localized more along the mid left sternal border. It is predominantly systolic with occasionally some slight spillover into diastole. The very rare small aortic pulmonary window does have a continuous murmur. The x-ray and ECG findings may be similar to the ductus. When considered and specifically looked for, the echocardiogram should visualize the window. The Doppler, however, will pick up abnormal continuous flow in the pulmonary artery similar to the ductus.

The confusion in diagnosis may persist during cardiac catheterization when an increase in oxygen saturation occurs in the main pulmonary artery. Although the right heart catheter, in an aortic pulmonary window, will pass from the main pulmonary artery into the *ascending* aorta and usually from there into a carotid vessel, it can pass from the ascending aorta around the arch and into the descending aorta giving a similar-appearing course to the ductus passage. Only a high-quality aortic angiocardiogram can absolutely separate the two lesions. Contrast injected in the aortic root often will spill so rapidly through the defect and into the pulmonary circuit that the details of the defect will be obscured. With an isolated aortic pulmonary window the descending aorta in the area of the ductus will appear intact with an injection into the descending aorta just distal to the usual entrance of the ductus. Contrast passing into the pulmonary artery first will pass retrograde around the arch with some filling of all of the brachiocephalic vessels. With the ductus, this same injection should directly and clearly visualize the patent ductus and fill the pulmonary arteries without significant visualization of the brachiocephalic vessels or the aortic root.

Because of its clinical similarities, but much different implications in terms of management, the aortic pulmonary window must always be considered and definitively ruled out when a patent ductus is suspected.

Venous Hum

The most often confused clinical entity with the patent ductus by the inexperienced observer is the innocent venous hum. This "continuous murmur" is generated by the normal high velocity venous flow in the superior vena cava of a child or patient with high cardiac output. The venous hum most frequently is localized in the first and second *right* intercostal spaces but can be heard on both sides. It has a more superficial sound, diastolic accentuation, marked change in quality with patient position, and can be obliterated by placing the patient supine and/or by gentle compression over the right or both jugular veins. All laboratory studies will be normal.

Truncus Arteriosus

The truncus arteriosus may occasionally be confused with a patent ductus because of the bounding or collapsing pulses and a murmur that may spill over from systole into diastole. The usual truncus arteriosus will present in early infancy before one month of age with profound heart failure. These infants will have a pansystolic or decrescendo systolic murmur that may spill into diastole and radiate over the lung fields. The patient will have collapsing pulses. Characteristically, they also have a very prominent ejection click and usually a single second heart sound on auscultation. The chest x-ray will show massive cardiomegaly and increased vascular markings. The electrocardiogram, more often, will show right or biventricular hypertrophy, but may show only left ventricular hypertrophy similar to the ductus. These infants will have varying degrees of desaturation that may or may not be clinically detectable, but should be demonstrated by ear oximetry

or cutaneous oximetry. The echocardiogram should clearly demonstrate the truncus arteriosus, which can be confirmed by catheterization and a quality ascending aorta (truncus) angiocardiogram. This will demonstrate the single semilunar valve and the aortopulmonary communication.

The rare infant with truncus arteriosus and some degree of right or left pulmonary stenosis may have a more characteristic continuous murmur. These infants are usually in less heart failure, but are more desaturated. The remainder of the differential is the same.

Absent Pulmonary Valve Syndrome

Infants with this combination of lesions usually present early in life with severe respiratory difficulty. On examination, they will have a characteristic to-and-fro separated systolic and diastolic murmur rather than the typical continuous or machinery murmur of the ductus arteriosus. This to-and-fro murmur is located along the left sternal border. They may or may not have an ejection click in association with this murmur. The electrocardiogram shows right axis deviation and right ventricular hypertrophy. The chest x-ray usually will show a small or only slightly enlarged heart and frequently severe hyperexpansion of the lungs. This hyperexpansion often is asymmetrical with one lung being markedly overexpanded with resultant compression or atelectasis of the opposite lung. The echocardiogram may be difficult in these patients because of the hyperexpansion of the lung. When obtainable, it should establish the diagnoses of at least ventricular septal defect and annular pulmonary stenosis and should find no evidence of a ductus.

A rare patient with this lesion will present at an older age with predominant to-and-fro heart murmur. The electrocardiogram, again, will show right axis deviation and right ventricular hypertrophy and the roentgenogram will show a slightly enlarged heart but with very prominent right and left hilar pulmonary vessels.

Cardiac catheterization will demonstrate hemodynamic findings similar to a "pink tetralogy" with less severe pulmonic stenosis. A right ventricular angiocardiogram will clearly show the annular stenosis, the ventricular septal defect, and the markedly dilated pulmonary arteries.

Ventricular Septal Defect with Aortic Regurgitation

Patients with ventricular septal defect and aortic regurgitation usually present with this combination of defects at a later age. If the patient has been previously known or evaluated, he or she may well have had a ventricular septal defect previously documented by echocardiogram and/or catheterization. Very often the ventricular septal defect is considered to be small. The patient returns with the new finding of a long diastolic murmur in addition to his earlier recognized pansystolic murmur. The examination at this time may reveal a systolic thrill along the sternal border and a pansystolic plateau-shaped murmur along the entire left sternal border, ending at the second sound. The second sound is increased and followed by a high-pitched, long decrescendo diastolic murmur that radiates down the left sternal border.[48] The frequency, length, and intensity of this diastolic murmur will depend on the degree of aortic regurgitation. As opposed to the persistent ductus arteriosus where the murmur crescendos up to the second sound and spills over into diastole, the murmur of ventricular septal defect with aortic regurgitation appears as two separate distinct murmurs with different frequencies and with almost a pause appearing between the systolic and diastolic components. There may be a diastolic rumble at the apex from either the increased flow of the ventricular septal defect and/or an Austin Flint type rumble from the aortic regurgitation. The peripheral pulses will be increased according to the severity of the aortic regurgitation as will the pulse pressure on blood pressure determination. On electrocardiogram, the patient may have biventricular hypertrophy or with long-standing aortic regurgitation, left ventricular hypertrophy. Roentgenography will show cardiomegaly proportionate to the earlier degree of shunting and to the degree of aortic regurgitation. The diagnosis should be documented by a high-quality echocardiogram specifically looking for the location of the ventricular defect and the degree of aortic regurgitation.

Ruptured Sinus of Valsalva and Fistula

The ruptured sinus of Valsalva is usually acquired later in life,[49] usually with no previous history of heart disease. It may occur spontaneously, following chest wall trauma or an episode of bacterial endocarditis. The onset is usually sudden or acute with the appearance of a loud, relatively superficial-sounding continuous murmur and often the associated appearance of significant congestive heart failure. On auscultation, the murmur is usually superficial sounding and more often localized over the lower sternum, particularly to the right of the midline.[49] The electrocardiogram may be normal or show early left ventricular strain. The chest x-ray, with a hemodynamically significant ruptured sinus and fistula, will show cardiomegaly and increased pulmonary flow. The echocardiogram may be able to document this lesion, but the definitive diagnosis should be by cardiac catheterization with an aortic root angiocardiogram.

Systemic Arteriovenous Fistula

Systemic arteriovenous fistula within the thorax can occur between any arterial and venous structures. Examples that may be confused with a patent ductus are communications between subclavian artery and innominate vein, between the internal mammary artery and vein, between bronchial arteries and branches of the systemic azygous system, or communications between other chest wall vessels. These communications do result in a continuous murmur; however, the murmur usually is localized to the area of the abnormal communication and appears more superficial and actually extracardiac in its location. The localization of the murmur depends on the point of communication between the vein and the artery. The systemic signs and symptoms depend on the size of the communication and the net shunt at that level. The differential from a patent ductus is usually obvious by the distant or separate location of the fistulous murmur. It will require a catheterization with an angiocardiogram to specifically localize the area of communication.

A variation in the usual systemic arteriovenous fistulae is the systemic to pulmonary artery fistula not associated with other significant congenital heart defects. The net hemodynamic effect is similar to a patent ductus. With the "venous end" of the fistulous vessel being the pulmonary artery or its branches, the clinical differentiation from a persistent ductus may be impossible prior to an angiocardiogram (Fig. 61–9).

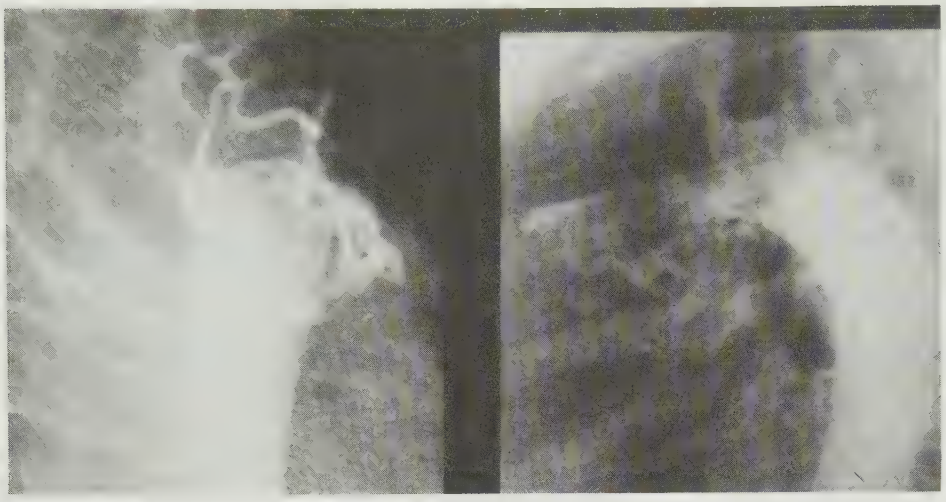

Fig. 61–9. Posteroanterior and lateral descending aorta aortograms showing a plexiform network of arteriopulmonary fistulous vessels actually encircling and eventually emptying into the main pulmonary artery. The clinical presentation in this patient was a high-pitched continuous murmur indistinguishable in location and quality from a small patent ductus.

Coronary Artery Fistula

Coronary artery fistulae produce a continuous murmur that is characteristically localized over the area of fistulous communication into the heart. In most cases, these are over the lower precordium and localized to the far right or left precordium away from the characteristic ductal area. The murmurs in these cases typically are continuous, but like the other systemic arteriovenous fistulae appear superficial on auscultation and usually are localized away from the site of the typical ductus murmur. The diagnosis usually is suspected from auscultation; however, it requires a cardiac catheterization and angiocardiograms to identify the area of fistulous communication specifically.

Pulmonary Arteriovenous Fistula

Pulmonary arteriovenous fistulae are usually multiple and often associated with multiple telangiectasia and at least mild cyanosis. The pulmonary atriovenous fistulae that do produce continuous murmurs over the lung field are usually larger and produce more marked cyanosis. The diagnosis is supported by the distribution of the murmurs, the cyanosis, and the right ventricular hypertrophy on electrocardiogram. The roentgenogram may show discrete densities throughout the lung fields. Confirmation of the diagnosis requires cardiac catheterization and pulmonary arteriograms.

Branch Pulmonary Artery Stenosis

Peripheral branch pulmonary artery stenosis may produce a continuous murmur. The murmur usually is later in onset continuing past the second sound into diastole. It is maximal over the peripheral lung fields, although it may be maximal over the left anterior chest in a similar location to the ductus arteriosus. Aside from the usual wide distribution of the murmur over the lung fields, these patients will have right ventricular hypertrophy on the electrocardiogram. The peripheral branch stenoses are usually difficult to visualize and quantitate by echocardiogram and will require cardiac catheterization with selective pulmonary angiography to delineate the defects exactly.

Systemic Collaterals with Pulmonary Atresia and Ventricular Septal Defect

The large systemic collaterals associated with pulmonary atresia type lesions do create loud continuous murmurs. These murmurs are usually localized in the vicinity of the lobes or lobules of the lungs supplied by the laterals, and thus, in general, are away from the area of the typical ductus murmur. Although most of these patients will be obviously cyanotic, those with large collaterals may present with congestive heart failure and nonclinically detectable cyanosis. Laboratory investigations, however, quickly separate these lesions. The majority of these patients have right ventricular hypertrophy, or at the least, biventricular hypertrophy on their electrocardiogram. They will have cardiomegaly, but characteristically with a concavity or deficiency in the area of the right ventricular outflow tract. These defects are thus easy to differentiate from a patent ductus on clinical grounds; however, the exact definition of the details of the collateral vessels will require an extensive and detailed catheterization with selective angiocardiograms.

DUCTUS ARTERIOSUS IN ASSOCIATION WITH ADDITIONAL, MORE COMPLEX LESIONS

The association of the persistent ductus with other defects has been alluded to earlier in this chapter. As a normally occurring structure in all infants and as a defect that is encouraged by the environmental circumstances found in association with many severe congenital heart defects, it is not surprising that it occurs in association with a high percentage of other congenital cardiac defects. The patent ductus may exist as a coincidental lesion possibly only complicating the other major lesion at the time of open heart surgery for the major lesion. More often, the shunting from the persistent ductus will aggravate the hemodynamics of the other lesion. At the other extreme, because of the complex anatomic variations and the abnormal hemodynamics of the major lesions, the survival of the patient may actually be dependent upon the ductus.

Aggravating Other Lesions

The major lesions aggravated by the persistent ductus are the other left-to-right shunt lesions where the ductus contributes more pulmonary flow to an already flooded pulmonary bed. The actual recognition of the combined defects is difficult enough, but often an even greater problem is the determination of which lesion is the most significant hemodynamically and then the choice of the

proper sequence of therapy. The primary example of this is the ductus coexisting with a ventricular septal defect. At catheterization, the systolic pressures in the right ventricle, pulmonary artery, left ventricle, and aorta are frequently equal and of no discriminatory value. Oxygen data will often reveal such a large increase in saturation at the ventricular level that even a large ductus will not show a significant further increase in saturation. For these combined shunt lesions, the best information comes from the visualization of the relative size of and flow through the defects by very high-quality cineangiocardiograms with injections immediately adjacent to the origin of each shunt lesion (i.e., in the left ventricle to visualize the ventricular septal defect or in the descending aorta to visualize the ductus). Other combined shunt lesions in this category include a ductus in combination with an atrial septal defect, an atrioventricular canal, or a combination of several of these.

Other lesions that a patent ductus will aggravate hemodynamically and symptomatically are the left heart inflow and/or left heart outflow obstructive lesions. The relative significance of the separate lesions can usually be determined from carefully acquired hemodynamics.

In the case of major intracardiac lesions significantly aggravated by the coexisting ductus, separate early correction of the more easily approached patent ductus usually is recommended. By this sequence, one can improve heart failure and gain time and growth before undertaking the repair of the major intracardiac lesion. In patients large enough for the use of the ductus occluding device, this approach is even more desirable.

Ductus-Dependent Lesions

At the other extreme of cardiac defects associated with a persistent ductus are those lesions where the infant's survival is dependent upon the continued patency of the ductus or a similar structure. These lesions must be accurately and expeditiously identified so that nothing is done to compromise the patency of the ductus. In the newborn period, efforts are made to keep the ductus open using pharmacologic agents such as prostaglandins until a surgical communication can be created to replace the function of the ductus.[50] There are opposite categories of patients that fall into the category of ductus-dependent lesions.

Cyanotic patients with severe or total ventricular to pulmonary artery outflow obstruction, with or without pulmonary artery hypoplasia, make up the first group. In these patients the total *pulmonary* flow is dependent upon the ductus.[51] These patients include those with any defects associated with pulmonary atresia (both with intact septum and with a ventricular septal defect) and many cases of tricuspid atresia where the interventricular communication is restrictive or there is additional right ventricular outflow obstruction. Patients with transposition of the great arteries or ventricular inversion who also have critical obstruction of the outflow to the pulmonary artery from the left ventricle, may fall into this category of ductus dependency.[51]

The second major category of totally ductus-dependent lesions are the patients with critical obstruction to *systemic* ventricular outflow or to part of systemic circulation and where the *systemic* flow or a significant part of the systemic flow is dependent upon the ductus. The most extreme degree of this type of lesion is the patient with aortic valve atresia and/or mitral valve atresia with a hypoplastic left ventricle where all systemic blood flow is from the right ventricle via the ductus arteriosus. With closure of the ductus, systemic flow is entirely stopped.

A second group of patients with systemic flow dependent on the ductus are those with only part of systemic flow obstructed and dependent upon the ductus—those patients with coarctation of the aorta or interruption of the aortic arch.[51,52] In most of these patients, when the ductus closes, there is decrease or cessation of blood flow to the lower half of the body. In the interrupted aortic arch and at least partially in the coarctation, this is due to the actual cessation of flow from the right ventricle to the descending aorta. In the coarctation of the aorta there is a second important role played by the ductus. The outpouching of the open aortic end of the ductus serves as a detour channel around the adjacent obstruction of the aorta caused by the posterior coarctation "shelf." This mechanism has been demonstrated both hemodynamically and angiographically and is the mechanism of the beneficial effect of prostaglandins in treating newborn patients with coarctation of the aorta and heart failure.

MANAGEMENT AND THERAPY OF DUCTUS

Medical Management

The usual patient with patent ductus is asymptomatic, presents with an incidental murmur, and requires no acute medical management. Those infants who do present with signs of congestive heart failure usually will respond to the usual decongestive regime including digoxin and diuretic therapy and on such a regime can be managed until they are several years old and good candidates for nonsurgical closure. When medical management fails in infancy, these patients are referred to surgery.

Surgical Management

In addition to these small infants, the policy at Texas Children's Hospital in the past was to refer any patient for surgical correction who had congestive heart failure that was refractory or poorly responsive to medical management regardless of the age or weight of the patient. Similarly in the past, most patients with asymptomatic patent ductus were referred for elective surgical ligation and division after they reached 4 or 5 years of age. By that age, the patients were beyond the age range where intubation created extra problems, they were slightly more understanding, and they reacted more favorably psychologically with primarily only "topical" fears. Some institutions recommend surgical repair of a patent ductus for any evidence of heart failure or electively at any time after 12 months of age, while others electively close the ductus whenever it is discovered, as it will need to be done sometime and is an easy operation.

Repair of the ductus does not require the use of cardiopulmonary bypass. The surgical approach to the typical persistent ductus ideally is through a left posterolateral thoracotomy incision in the third intercostal space in infancy or fourth left intercostal space in patients past infancy. Once the ductus is identified and dissected free from the surrounding tissues, it is ligated at both the aortic and pulmonary artery ends and divided between the sutures. The postoperative thoracotomy patients usually require a chest tube for 24 hours and a hospital convalescence of 6 to 7 days. Once discharged, these patients require an additional 6 to 8 weeks before they can return to full, unrestricted physical activity.

Fig. 61–10. Rashkind Ductal Occluding Device® of 12-mm diameter shown in the side and frontal view. The side view (left) shows the two opposing umbrellas opened against each other. The frontal view (right) shows the surface of the fabric and the three arms of the one umbrella.

The surgical repair of the ductus is considered "easy" and "safe" and does carry a low, but not absent, morbidity or mortality.[53,54] Cases of "recanalization," or more likely incomplete initial ligation,[55,56] have occurred with persistence of the ductus following only surgical ligation. With the more detailed and sophisticated techniques of evaluating these patients using color-flow Doppler, the incidence of this may prove to be higher. As with any thoracic surgical procedure, bleeding, which can be extensive, may occur. More specific to the surgery for the persistent ductus, injury to the recurrent laryngeal nerve or disruption of the thoracic duct with resultant chylothorax has been reported. The more serious complications of surgical repair of the ductus include ligation of the left pulmonary artery, the descending aorta, or even a carotid artery instead of the ductus, all with potentially catastrophic results.

Catheter Closure of Patent Ductus

The advent of a catheter technique for closure of the patent ductus[57] already has changed these policies at Texas Children's Hospital and undoubtedly will soon affect the policies of most progressive institutions in the world. The small infant weighing less than 7 or 8 kg with a large persistent ductus and in refractory heart failure is now the only unequivocal indication for surgical repair of a ductus.

Dr. Werner Porstmann first devised a catheter-delivered device for the nonsurgical closure of a patent ductus.[58,59] This device required a very large and complicated combined arterial and venous delivery system. Although still in use in a few locations for larger patients, it never gained much general popularity or use. Dr. William Rashkind developed a completely different and smaller device and system for transcatheter closure of the persistent ductus arteriosus.[60] After numerous modifications, his device was introduced into clinical trials in 1981. The details of the technique are discussed in Chapter 130 on Therapeutic Catheterizations.

The Rashkind Ductus Occlusion Device® is comprised of two small fabric umbrellas on stainless steel frames. The two umbrellas are connected together at the centers by a spring mechanism that holds the umbrellas in the open position in opposition to each other (Fig. 61–10). The occlusion device is delivered to the ductus through a special 8 French delivery catheter from either the atrial or venous route. The device is positioned in the ductus with one umbrella on the aortic end and the other umbrella on the pulmonary end of the ductus. When released in this location, the opposing umbrellas occlude flow through the ductus (Fig. 61–11).

As a part of the original collaborative clinical trials, the device has been used in 150 patients at Texas Children's Hospital with an overall success rate of over 80% total occlusion and with no complications from the device or the delivery procedure. The majority of the "failures" occurring now are hemodynamically insignificant, *inaudible* residual ductus only detectable by high-quality color-flow Doppler techniques. The nonsurgical closure of the ductus is now the recommended initial therapy for all patients with ductus who can be medically managed until they are at least 8 kg in weight. The patient undergoing transcatheter closure of the ductus spends the night following catheterization in the hospital and is discharged to full normal physical activity the following day. The only disadvantage to the nonsurgical approach is that if it cannot be accomplished, the patient will still require surgery to correct the ductus.

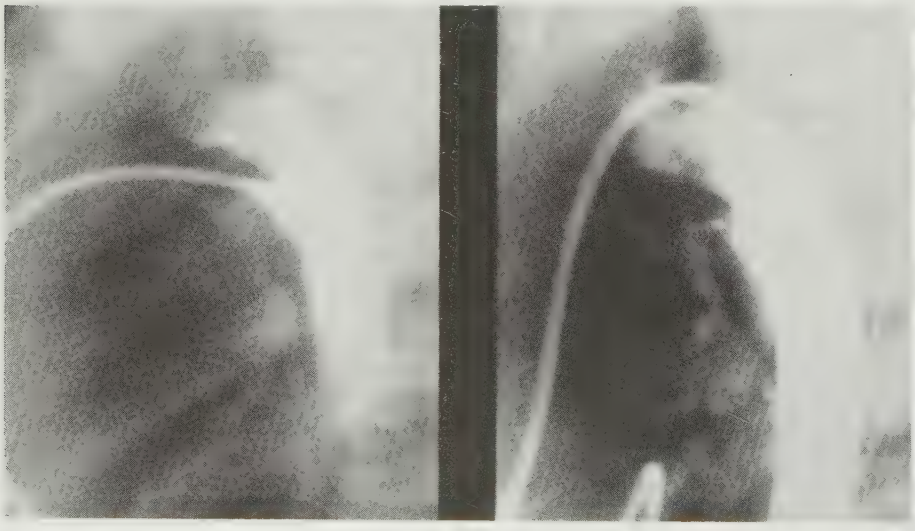

Fig. 61–11. Two comparable lateral descending aortograms showing (left) a catheter passing through a patent ductus, and (right) the same ductus totally occluded by the Rashkind Ductal Occluding Device.

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CHAPTER 62

Clinical Physiology of Right-to-Left Shunts

J Timothy Bricker

Tetralogy of Fallot can be considered the archetype of right-to-left shunt physiology. In the patient with tetralogy of Fallot, a large interventricular communication is present with a restriction to pulmonary blood flow. The degree of hypoxemia ranges from slight to profound. The amount of obstruction of flow into the pulmonary arteries is the major factor determining the degree of hypoxemia. Other lesions, such as a single ventricle with pulmonary stenosis, can be thought of as "tetralogy physiology."

As stated in Chapter 58, it is relatively easy to reduce complex congenital cardiac defects into one of four physiologic types: left-to-right shunt physiology, right-to-left shunt physiology, transposition physiology, and the physiology of obstructive and regurgitant lesions without shunts. A great many malformations can be considered under the category of right-to-left shunt physiology.

In the patient with a right-to-left shunt, the blood flow to the pulmonary capillary bed is lower than the flow to the systemic capillary bed. The differences between these two flows equals the amount of deoxygenated blood that is shunted from the right-sided (systemic venous) return to the left-sided (systemic arterial) circulation and is, by definition, the right-to-left shunt (Table 62–1). Calculation of the right-to-left shunt flow at cardiac catheterization is done by subtracting the systemic blood flow from the effective pulmonary blood flow. Systemic and pulmonary flows are calculated from the Fick equation based on measured saturations, oxygen consumption, and hemoglobin as discussed in Chapter 54. It is also possible to calculate a systemic-to-pulmonary flow ratio without calculation of flow (Table 62–1). A right-to-left shunt may occur at the level of the atria, ventricles, great vessels, or pulmonary microcirculation. The clinical consequences of a right-to-left shunt depend upon both the magnitude and the location of the shunt. In addition, the chronicity of the physiologic state and the adequacy of compensation are important factors in the clinical manifestations of a right-to-left shunt. Consequences of severe hypoxemia are discussed in greater detail in Chapter 116.

DETERMINANTS OF THE DEGREE OF RIGHT-TO-LEFT SHUNT AND OF CYANOSIS

The amount of obstruction to pulmonary flow is the usual major determinant of the magnitude of a right-to-left shunt. This obstruction may be at any of a number of different levels. For example, the obstruction to pulmonary blood flow is at the level of the tricuspid valve for the patient with tricuspid stenosis and an atrial septal defect. Muscular subpulmonic obstruction in the patient with a ventricular septal defect is a common cause of a ventricular level right-to-left shunt. Mid-ventricular obstruction (e.g., from a right ventricular muscle bundle) may also cause a right-to-left shunt at the ventricular level if there is a muscular ventricular septal defect. Obstruction to pulmonary blood flow may be at the level of the pulmonary valve. Pulmonary stenosis with an intact atrial and ventricular septum does not result in right-to-left physiology. Pulmonary stenosis, if severe, will result in right-to-left physiology for the patient with a ventricular septal defect or single ventricle. If critical pulmonary stenosis causes right ventricular dysfunction, one may find right-to-left physiology from an atrial level shunt.

Descriptions of cyanotic lesions by Fallot included patients with severe pulmonary stenosis, right ventricular hypertrophy, and atrial septal defect (which is still called trilogy of Fallot by some).

Table 62–1. Calculation of Right-to-Left Shunt

1. Right-to-left shunt $= Q_s - Q_{ep}$
2. Q_s = systemic blood flow $= \dfrac{\text{Oxygen uptake}}{(\text{Aorta } O_2 \text{ content} - \text{Mixed venous } O_2 \text{ content})}$
3. Q_{ep} = effective pulmonary blood flow $= \dfrac{\text{Oxygen uptake}}{(\text{Pulmonary venous } O_2 \text{ content} - \text{Mixed venous } O_2 \text{ content})}$
4. Pulmonary to systemic flow ratio $= Q_p/Q_s = \dfrac{\text{Aorta saturation} - \text{Mixed venous saturation}}{\text{Pulmonary vein saturation} - \text{Pulmonary artery saturation}}$

Obstruction at the level of the pulmonary valve with an intact ventricular septum, right ventricular dysfunction, and a patent foramen ovale may result in an atrial level right-to-left shunt for the neonate with critical pulmonary stenosis or for the adult who had closed valvotomy (Brock procedure) in childhood. Obstruction to pulmonary blood flow resulting in right-to-left physiology can be within the pulmonary arterial bed. Supravalvular pulmonary stenosis, bifurcational stenosis, main pulmonary artery stenosis, distal pulmonary artery stenosis, or diffuse hypoplasia of the pulmonary arteries may be the reason pulmonary blood flow is limited. Primary pulmonary hypertension or pulmonary vascular obstructive disease may result in right-to-left physiology in patients with an intracardiac communication. Thus, the patient who develops Eisenmenger reaction from a large left-to-right shunt eventually acquires the physiology of a right-to-left shunt. Patients with primary pulmonary hypertension and a patent foramen ovale have been known to present with unexplained cyanosis. If the pulmonary blood flow is supplied from the aorta, obstruction to pulmonary blood flow can increase if the ductus arteriosus closes, if aorticopulmonary collaterals become stenotic, or if an aorticopulmonary anastomosis that the surgeon has created becomes narrowed.

Although the typical patient with a right-to-left shunt is hypoxemic, this is not always so. For example, the patient with "pink tetralogy" (the acyanotic form of tetralogy of Fallot) may have a well-matched left-to-right and right-to-left shunt resulting in minimal or no hypoxemia. With this situation, the pulmonary blood flow is normal or even increased. Even though there is an intracardiac right-to-left shunt in the patient with "pink tetralogy" the degree of obstruction to pulmonary blood flow is slight and the pulmonary-to-systemic flow ratio may be normal. More complicated cardiac lesions with both right-to-left and left-to-right shunts may also be well balanced like the acyanotic tetralogy patient. The newborn with single ventricle and mild to moderate pulmonary stenosis, for example, is often physiologically well balanced. This baby may eventually require a pulmonary artery banding after the pulmonary vascular resistance drops if the pulmonary obstruction remains slight, or might need an operation for creation of a systemic to pulmonary artery shunt if pulmonary obstruction increases, or the baby may do well with no surgical intervention in infancy if the pulmonary and systemic flows remain well balanced. Thus it can be seen that the amount of right-to-left shunt can change with time depending upon the severity of obstruction to pulmonary blood flow and that this progression of severity of right-to-left shunt cannot be precisely predicted for an individual patient.

There are factors other than obstruction to pulmonary blood flow that alter the amount of right-to-left shunting. An abrupt increase in right-to-left shunt may result in a severe hypoxemia associated with hyperpnea, irritability, and intense cyanosis. Various factors such as crying, hyperpnea, and hypoxemia itself serve to perpetuate an episode of increased cyanosis. These episodes have been referred to as "tetralogy spells" (or "tet spells" in the jargon of the ward). Other terms that have been used for these episodes have included hypercyanotic spells, anoxic spells, paroxysmal dyspnea, and hyperpneic spells. In spite of the name "tet spells," these episodes occur in settings with right-to-left physiology other than tetralogy of Fallot. Although it was once thought that "spasm" of the infundibulum was the cause of these spells in tetralogy of Fallot, it is clear that hypercyanotic spells can occur in patients who do not have infundibular stenosis (or even an infundibulum). Although hypercyanotic spells are discussed elsewhere in this text, it is instructive to review some of the factors that may initiate a hypercyanotic spell in the context of the physiologic determinants of the degree of right-to-left shunting.

One of the physiologic changes that usually increases hypoxemia in patients with right-to-left physiology (and may precipitate hypercyanotic spells in patients at risk) is vasodilation of the systemic vascular bed. A comment sometimes obtained in the history is that a baby is more blue after a warm bath. We often note an increase in hypoxemia if a drug with vasodilating properties is administered (such as Thorazine for sedation). Sometimes an increase in cyanosis is observed with the vasodilation from a fever or exanthem. The vasodilation that occurs during exercise is one of the factors that transiently increases hypoxemia for patients with right-to-left physiology. Preferential runoff into the distal systemic capillary bed rather than into the pulmonary artery increases hypoxemia in the patient whose pulmonary flow depends on small aorticopulmonary connections. Changes in peripheral vascular resistance can also alter shunting in patients with right-to-left physiology who do not have aorticopulmonary connections. The effect is probably by means of changes in ventricular volumes and by causing a relative hypovolemia. Efforts to treat or prevent hypercyanotic spells have employed the relationship between systemic resistance and the magnitude of the right-to-left shunt. Older children with right-to-left physiology and severe hypoxemia may learn to squat to improve symptoms while at play. The major benefit to them is probably due to the increase in aortic afterload from kinking the femoral arteries (although other explanations have been proposed). The equivalent of this maneuver for the infant is the use of the knee-chest position to improve arterial saturation during a hypercyanotic spell. Neo-synephrine will improve arterial oxygen saturation during a hypercyanotic spell by constriction of the systemic arteriolar bed. Ketamine is often used as an anesthetic during cardiac catheterization of children with a right-to-left shunt because of the peripheral vasoconstriction which occurs with the use of this drug.

Intrathoracic pressure can affect the degree of right-to-left shunt in some patients. If the limitation to pulmonary blood flow is extreme, the small trickle of blood into low-pressure pulmonary arteries could be further diminshed by a high pressure surrounding those vessels. Examples of an increase in intrathoracic pressure affecting a right-to-left shunt could include crying, hyperpnea, Valsalva maneuver, exercise, obstructive or restrictive lung disease, and mechanical ventilation.

Tachycardia can increase the right-to-left shunt. Plausible mechanisms include changes in the amount of obstruction, a decrease in intravascular volume, or changes in the systemic vascular resistance due to the tachycardia. Supraventricular tachycardia or sinus tachycardia potentially will precipitate hypercyanotic spells. Decreasing the heart rate (by soothing the infant, by sedation, by cardiac reflexes associated with volume increase or arterial blood pressure increase, or by propranolol) can be employed in efforts to prevent or treat hypercyanotic spells.

The patient's blood volume is also a factor in the amount of right-to-left shunt. Dehydration from diarrhea or diuresis increases the hypoxemia of the infant with a cyanotic cardiac defect. Volume infusion can be effective in the treatment and prevention of hypercyanotic spells. The blood volume can affect the anatomic degree of obstruction by means of changes in intracardiac volumes. In addition, hypovolemia is related to tachycardia and the systemic vascular resistance.

Hypoxemia and cyanosis result from a right-to-left shunt of any magnitude. Cyanosis depends on not only the arterial saturation but also the hemoglobin level. Five grams of desaturated hemoglobin per deciliter of blood are required for the child to appear cyanotic. For example, the infant with the physiology of a right-to-left shunt who has a hemoglobin of 10 g/dL would not appear cyanotic to the examiner until the arterial saturation is about 50%. This infant can have a significantly impaired oxygen delivery to the body without a blue appearance on examination. Thus hypoxemia out of proportion to the observed cyanosis can exist in the patient who has a low hematocrit. In the same respect, increasing the hemoglobin will, within limits, increase the arterial oxygen content at a given saturation. If the hemoglobin was increased to 20 g/dL by blood transfusion in this patient who remained at 50% arterial saturation, the blood oxygen content would double although the child would appear much more cyanotic. An additional factor is that increasing the blood volume may increase the cardiac output, which would be likely to improve the pulmonary blood flow and increase the total systemic blood flow that serves to increase the delivery of oxygen to the total body.

COMPLICATIONS AND SEQUELAE OF RIGHT-TO-LEFT SHUNTS

The patient with an intracardiac right-to-left shunt is vulnerable to paradoxical embolization. If small emboli (such as clots or air bubbles from an intravenous line) occur in the systemic venous circulation, the result is small pulmonary emboli for the normal individual. These small pulmonary emboli generally do no harm and are not noticed. However, in the patient with a right-to-left shunt, embolization is likely to occur to the systemic arterial circulation with profound effects upon the patient. Emboli to the cerebral, coronary, mesenteric, or renal arterial beds may have important consequences. Amniotic fluid emboli during childbirth, for instance, can result in a devastating stroke. Efforts to prevent venous thromboembolic disease is particularly important in the patient with a right-to-left shunt. The use of air filters on intravenous lines is important to prevent air embolus. However, this cannot replace diligence in the prevention of air in intravenous tubing in these patients. One should be reluctant to use an intravenous line in the patient with a right-to-left shunt unless absolutely necessary because of the risk of paradoxical embolization. The use of a heparin lock in a patient with right-to-left shunt physiology has been avoided in our practice because of the belief that intermittent flushing may dislodge clots with a greater potential for paradoxical embolization than a carefully watched continuous intravenous infusion that has an air filter in line.

The hemoglobin level that is acceptable for the pediatric or neonatal patient with normal hemodynamics reflects a relative anemia for the child who is chronically hypoxemic because of a right-to-left shunt. The additional oxygen-carrying capacity that increases the efficiency of oxygen transport is limited by the circulatory disadvantages of polycythemia. At hematocrit levels over about 65%, the circulatory inefficiency of capillary sludging of blood outweighs the advantage from increases in oxygen-carrying capacity or further increases in the red blood cell volume. Excessive polycythemia causes symptoms of lethargy, headaches, joint pains, and overt neurologic abnormalities on occasion.

The patient with a right-to-left shunt is at risk for a brain abscess. The source of intracerebral abscesses in patients with a right-to-left shunt is typically from hematogenous spread rather than direct extension. Although organisms similar to those that cause endocarditis may cause brain abscesses, intracerebral abscesses may be due to anaerobic organisms or grow mixed flora as discussed by Patrick and Kaplan in Chapter 148 of this text.

Renal abnormalities in chronic hypoxemia from a right-to-left shunt are reviewed by Berry in Chapter 146. The usual finding is glomerulomegaly, which is typically associated with minimal or no functional abnormalities although hematuria or proteinuria is occasionally found.

Hypertrophic osteoarthropathy is a result of severe hypoxemia as discussed in Chapter 147. Hypertrophic osteoarthropathy is of more cosmetic consequence than functional importance. But for some adolescents with a right-to-left shunt, the cosmetic aspects of clubbing and cyanosis can be a devastating aspect of their cardiovascular handicap.

Chronic hypoxemia has direct cardiac effects as well. Hypoxemia on a chronic basis can result in myocardial function abnormalities and myocardial fibrosis histologically. Chronic hypoxemia has been associated with electrophysiologic abnormalities. This abnormality in cyanotic individuals may contribute to the postoperative arrhythmias found in this population. Preliminary data suggest that chronic hypoxemia may be a risk factor for the development of atherosclerotic disease.

CHAPTER 63

Tetralogy of Fallot and Tetralogy of Fallot with Pulmonary Atresia

William H Neches
Sang C Park
Jose A Ettedgui

The term tetralogy of Fallot refers to a spectrum of anatomic abnormalities that have a large and unrestrictive ventricular septal defect and right ventricular outflow tract obstruction. The clinical presentation varies from the asymptomatic acyanotic child with a heart murmur to the severely hypoxic newborn infant and depends largely on the nature and degree of this outflow obstruction. Although the anatomic features and clinical manifestations of this anomaly had been previously described, it was Fallot in 1888[1] who carefully detailed the clinical and pathologic correlations of this group of congenital cardiac malformations that he termed "maladie bleue" and which now bears his name. Over the ensuing 5 or 6 decades much was written about the clinical features, pathology, embryology, and natural history of tetralogy of Fallot, but is was not until 1945, with the development of systemic to pulmonary artery anastomoses,[2,3] that it became possible to improve and lengthen the life of patients with this abnormality. Ten years later, in 1955, Lillehei et al.[4] described the first successful repair of tetralogy and thus began the modern era of the surgical management of this lesion. Since there are a wide variety of anatomic abnormalities that produce a similar clinical picture, it seems appropriate to review the anatomic particulars of tetralogy of Fallot prior to any discussion of the clinical features, diagnosis, or management of patients with this disorder.

ANATOMIC CONSIDERATIONS

The earliest description of the conditions we refer to as the tetralogy of Fallot dates to the seventeenth century.[5] The eponym originated from the clinicopathologic correlations by Fallot in the late nineteenth century of a condition consisting of a ventricular septal defect, aortic override, pulmonary stenosis, and right ventricular hypertrophy.[1] The anatomic hallmark of the tetralogy of Fallot is the anterocephalad deviation of the outlet septum. Apart from producing infundibular pulmonary stenosis, this deviation accounts for the ventricular septal defect and the aortic override (Fig. 63–1). These anatomic features warrant a more detailed description. Their variability accounts for the wide spectrum of clinical and hemodynamic findings. It is currently accepted that hypertrophy of the right ventricle is the result of the underlying anatomic and hemodynamic abnormalities.

Right Ventricular Ouflow Tract and Pulmonary Arteries

In the normal heart, the outlet septum is positioned between the limbs of the septomarginal trabeculation and is undistinguishable from the ventriculoinfundibular fold. As mentioned earlier, anterocephalad deviation of the outlet septum in relation to the septomarginal trabeculation is the basic anatomic feature in tetralogy of Fallot. This deviation significantly narrows the right ventricular outflow tract and is responsible for most of the infundibular pulmonary stenosis (Fig. 63–2). Hypertrophy of the outlet septum, hypertrophy of muscle bundles extending into the anterior right ventricular free wall, and hypertrophy of the anterior limb of the septomarginal trabeculation contribute to the infundibular narrowing. The severity of infundibular obstruction ranges from mild to severe pulmonary stenosis to pulmonary atresia (Fig. 63–3). On occasion there can be an added obstruction within the body of the right ventricle, proximal to the stenotic infundibulum. This is produced by "anomalous muscle bundles" represented by hyper-

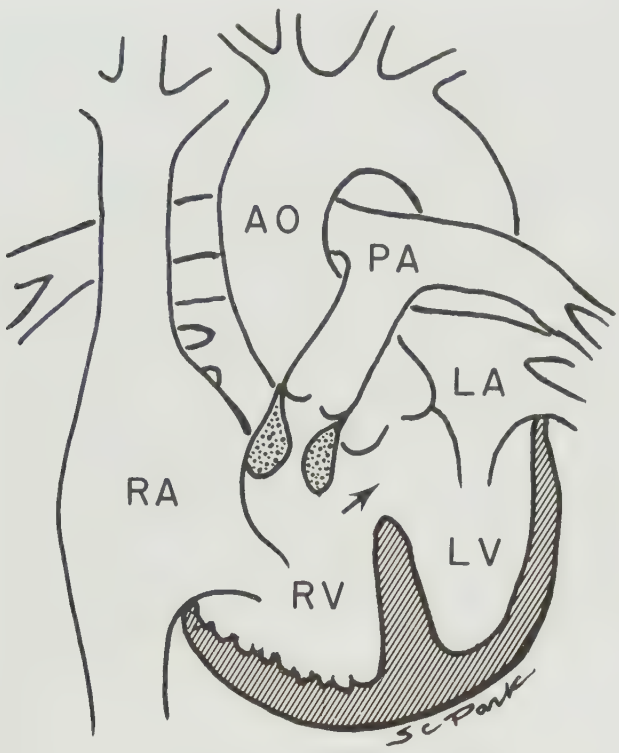

Fig. 63–1. Diagram illustrating the anatomic abnormalities in tetralogy of Fallot. Ao = Aorta; PA = Pulmonary artery; LA = Left atrium; RA = Right atrium; LV = Left ventricle; RV = Right ventricle. (These abbreviations are used in all illustrations.) Note the ventricular septal defect (arrow), infundibular pulmonary stenosis (stippled area), and the overriding aorta.

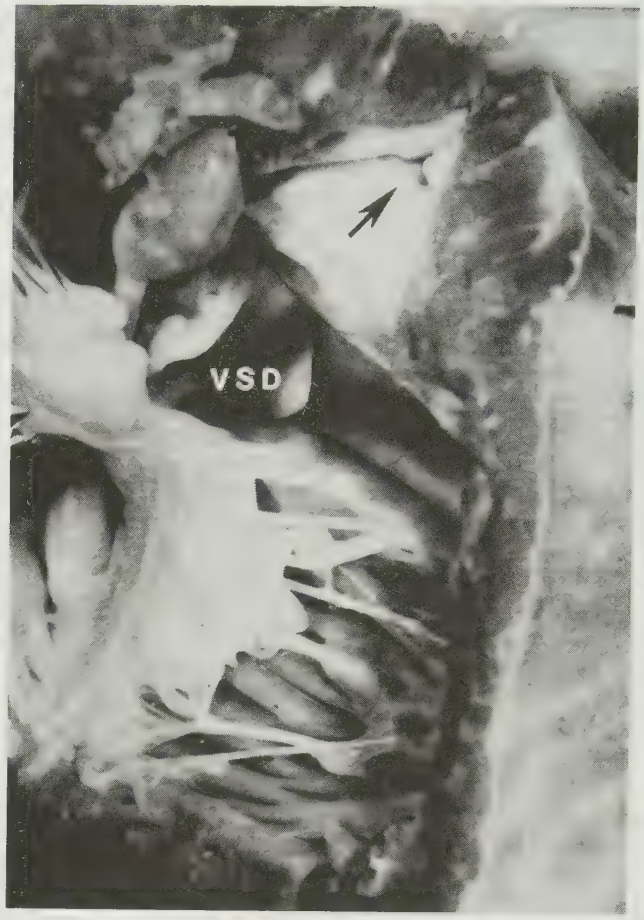

Fig. 63–2. Pathologic anatomy of tetralogy of Fallot (see text). Arrow = Infundibular pulmonary stenosis. VSD = Ventricular septal defect.

trophy of the apical component of the septomarginal trabeculation and other apical trabeculations.

Further obstruction to pulmonary blood flow often occurs at other levels (Fig. 63–4). Pulmonary valve stenosis is common[6,7] and can be due to a stenotic three leaflet, bicuspid, or unicuspid valve. Occasionally stenosis is the result of a small pulmonary valve "ring" or of supravalvar fibrous ridges. Stenoses at the origin of the right or left branch pulmonary arteries are common, and are usually amenable to surgical repair. Further narrowing in the distal branch pulmonary arteries may also occur but is more difficult to approach surgically.

One pulmonary artery may arise from the aortic arch instead of from the pulmonary trunk (Fig. 63–4). It is usually connected to the aorta through a patent ductus arteriosus or directly from the ascending aorta. The left pulmonary artery is more commonly affected than the right.[8–10] When the ductus closes, blood supply to the pulmonary artery becomes very limited and is usually through small collateral vessels. On the other hand, if the aortic communication remains widely patent, the pressure in the pulmonary artery may be at systemic level leading to the development of pulmonary vascular disease in the affected side.

Pulmonary Arteries and Collateral Circulation in Tetralogy of Fallot with Severe Pulmonary Stenosis or with Pulmonary Atresia

There is great variability in the anatomy of the pulmonary arteries and the source of pulmonary blood flow in tetralogy of Fallot with pulmonary atresia (Fig. 63–5). A fully developed, normal sized main pulmonary artery confluent with the right and left branches is not common. These central pulmonary arteries are usually small and hypoplastic. Angiographically they have a "seagull" appearance. More frequent possibilities include patent right and left pulmonary arteries that may be confluent with an absent main pulmonary artery, presence of one pulmonary artery with absence of the other, and finally, there may be complete absence of central pulmonary arteries. When present, the central pulmonary arteries are not necessarily connected to all of the intrapulmonary arterial segments. This creates the possibility of different lung segments having different sources of blood supply (i.e., collateral circulation). The intrapulmonary arteries, however, do not differ regardless of their connection to central pulmonary arteries or to collateral vessels.

Since there is no antegrade flow from the right ventricle to the pulmonary arteries, blood reaches the pulmonary vasculature through different routes. A patent ductus arteriosus is an important pathway that depends on the existence of central pulmonary arteries. In the presence of nonconfluent pulmonary arteries there may be bilateral ducti.

Another important source of pulmonary blood flow are major aortopulmonary collateral arteries. These vessels originate from

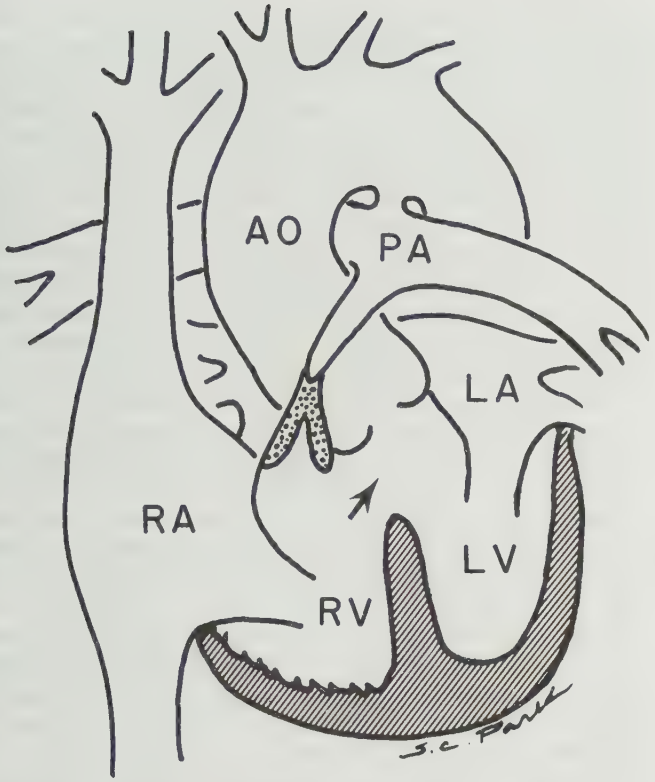

Fig. 63–3. Diagram illustrating the anatomic features of tetralogy of Fallot with pulmonary atresia. Ao = Aorta; PA = Pulmonary artery; LA = Left atrium; RA = Right atrium; LV = Left ventricle; RV = Right ventricle. Note the ventricular septal defect (arrow), infundibular and valvar atresia (stippled area), and hypoplastic main pulmonary segment. Pulmonary blood flow is via a patent ductus arteriosus.

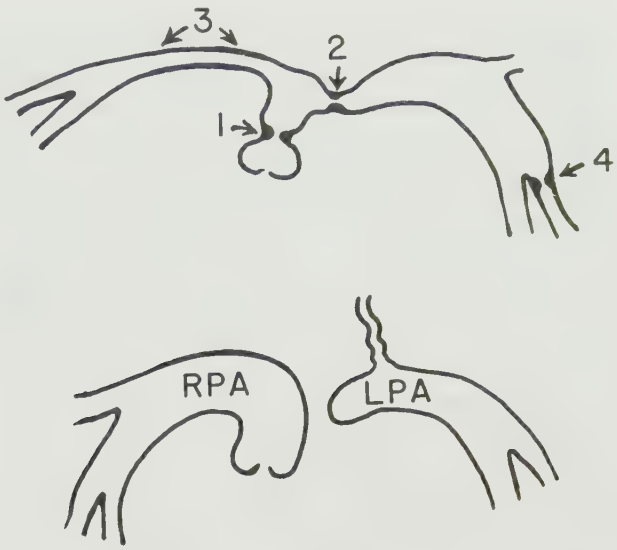

Fig. 63–4. Areas of pulmonary stenosis in tetralogy of Fallot. Top—Pulmonary artery stenosis: 1. Supravalvular stenosis; 2. Discrete pulmonary artery stenosis; 3. Tubular hypoplasia of a segment; 4. Distal arterial stenosis. Bottom—Discontinuity of the pulmonary arteries. The left pulmonary artery arises from a ductus arteriosus.

the intrathoracic portion of the descending aorta in the proximity of the left mainstem bronchus. Rarely, they may arise from the aortic arch or the subclavian artery. These vessels are embryologically and histologically different from bronchial arteries and ducti.[11–13] The number of collateral vessels is variable and they usually follow a tortuous course. They may anastomose to the central pulmonary arteries at the hilum or within the lung.[14] These aortopulmonary collaterals may directly supply blood to the intrapulmonary plexus in the absence of true pulmonary arteries. A collateral vessel may supply different segments of both lungs. Generally, the major aortopulmonary collateral arteries have stenoses in their course. The stenosis is usually located at the point of anastomosis to an intrapulmonary artery and histologically is produced by a mound of intimal tissue.[15] The severity of the stenosis is variable and occasionally some collateral arteries are unobstructed. The segments supplied by these vessels are at risk of developing pulmonary vascular disease.[12,14]

A third source of pulmonary blood flow is through acquired collateral arteries. These are multiple, small vessels that can originate from the bronchial arteries, intercostal arteries, and coronary arteries. Very rarely pulmonary blood flow is supplied through an aortopulmonary window.[16]

These multiple sources of pulmonary blood supply create the possibility of unifocal or multifocal pulmonary blood flow. Uni-

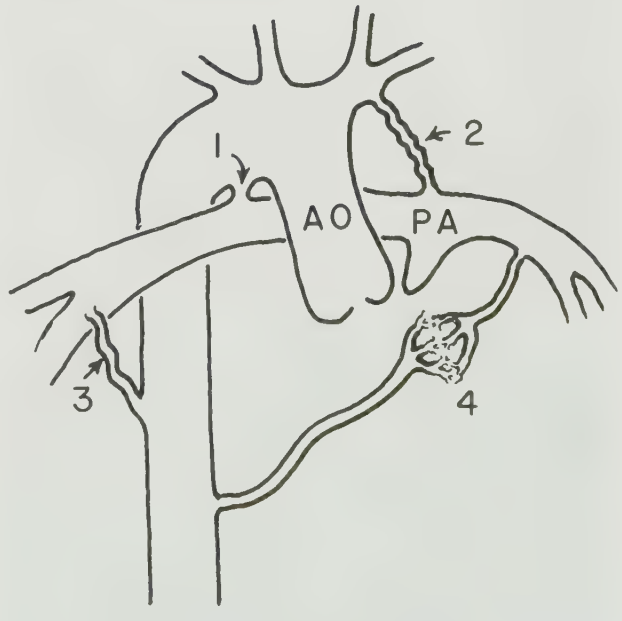

Fig. 63–5. Diagram of the pulmonary blood supply in tetralogy of Fallot with pulmonary atresia: 1. Ductus arteriosus from the descending aorta; 2. Ductus arteriosus from the innominate artery (left sided ductus is most common with a right aortic arch); 3. Aortopulmonary collateral vessel from the descending aorta; 4. Intercollateral anastomosis providing pulmonary blood flow.

focal pulmonary blood supply requires the presence of confluent pulmonary arteries, connected to all of the intrapulmonary arterial segments regardless of the origin of the flow to the true pulmonary arteries. Unifocal blood flow is very common in tetralogy of Fallot but is less frequent when there is associated pulmonary atresia.[17,18] In multifocal pulmonary blood supply the central pulmonary arteries, when present, are not connected to all of the intrapulmonary arterial segments of both lungs. There is a combination of lung segments supplied by central pulmonary arteries, segments supplied by major aortopulmonary collateral arteries and segments that have a dual supply[19] (see Fig. 63–3). This concept has relevance in the surgical management of patients with tetralogy of Fallot.

Ventricular Septal Defect

A large, unrestrictive malalignment ventricular septal defect is another of the consequences of the anterocephalad deviation of the outlet septum. The borders of the ventricular septal defect are the aortic valve leaflets and the ventriculoinfundibular fold superiorly, the fusion of the outlet septum to the anterior limb of the septomarginal trabeculation anteriorly, and the crest of the trabecular septum inferiorly[7] (Fig. 63–6). Of great surgical importance are the variations occurring along the posteroinferior margin of the defect. In 80% of patients this margin is the central fibrous body and the defect is therefore perimembranous. There will be fibrous continuity between the tricuspid valve and aortic valve through the ventricular septal defect. In 20% of patients there is a muscle bar along the posteroinferior rim of the defect separating the tricuspid valve from the aortic valve. In these cases the ventricular septal defect is muscular. The relevance of the distinction between a perimembranous and a muscular ventricular septal defect is related to the position of the penetrating bundle of His. In a perimembranous ventricular septal defect, the penetrating bundle runs along the posteroinferior margin of the defect and is at risk of being damaged at the time of surgical correction. In a muscular ventricular septal defect, the muscle bar along the posteroinferior rim of the defect provides a "cushion" or "safety margin" that allows the surgeon to suture the patch closing the ventricular septal defect with minimal risk of damaging the conduction tissues.

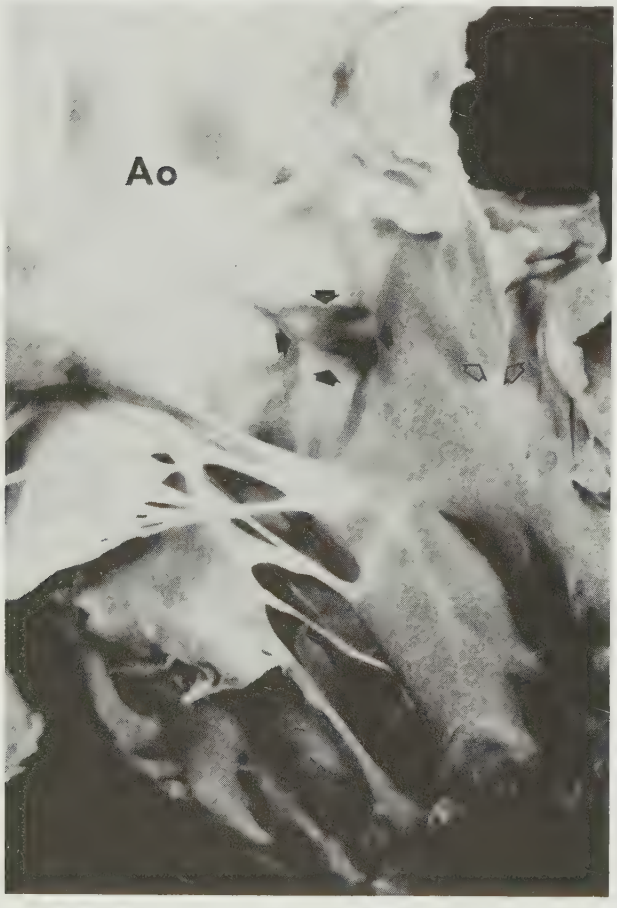

Fig. 63–6. Close up view of the ventricular septal defect in tetralogy of Fallot (see text). Closed arrows = Ventricular septal defect margins; Open arrows = Outlet septum.

In some patients the ventricular septal defect may extend into the inlet portion of the septum. In this situation, part of the tensor apparatus of the tricuspid valve extends into the left ventricle resulting in a straddling tricuspid valve.

An additional ventricular septal defect, or multiple defects, may be present in the trabecular portion of the intraventricular septum in from 3 to 15% of patients with tetralogy of Fallot.[20] Occasionally, a complete atrioventricular septal defect may coexist with the anterocephalad deviation of the outlet septum, therefore also falling in the category of the tetralogy of Fallot (i.e., tetralogy with AV canal).[21] These patients are a surgical challenge in view of the complexity of operative repair. A separate group of patients, often considered to have tetralogy of Fallot, are those that have a doubly committed subarterial ventricular septal defect.[22] In these hearts there is continuity between the aortic and pulmonary valves through the ventricular septal defect. For this type of defect to exist there has to be absence of the outlet septum. This obviously contradicts our definition of tetralogy of Fallot. Since in these patients pulmonary stenosis is the result of a small pulmonary valve "ring," we propose that these patients be considered separately from tetralogy of Fallot.

In a small number of patients with tetralogy of Fallot (less than 5%) the ventricular septal defect may be restrictive and produce suprasystemic right ventricular pressure. Since tetralogy is characterized by a large and unrestrictive defect, it would seem that these hearts do not meet this requirement. However, in almost all cases accessory or excessive tricuspid valve tissue has been found obstructing a large defect, often with anomalous attachments to the margins of the defect,[23,24] and the basic anatomy is otherwise similar to tetralogy.

Aortic Override

One way of avoiding the controversy over the existence of aortic override in the tetralogy of Fallot would be the term "biventricular aortic connection." This accurately describes the relation of the aorta to both right and left ventricles. However, the term aortic override continues to be valid.

In the normal heart, the right coronary sinus "overrides" the intact ventricular septum. The presence of a ventricular septal defect would create the impression of override. In tetralogy of Fallot, the aortic root may be dilated, further contributing to the impression of override.[25] This override has been demonstrated both

anatomically[26] and echocardiographically.[27] The degree of override ranges from 15 to 95%.[7] This extent of override raises the question of a double outlet right ventricle if more than 50% of the aorta is connected to the right ventricle. If a double outlet right ventricle is defined as an anatomic entity with a subaortic and subpulmonary infundibulum with discontinuity between the mitral and aortic valves, it obviously excludes the tetralogy of Fallot.[28,29]

Coronary Arteries

Abnormalities in the origin and distribution of the coronary arteries are common in the tetralogy of Fallot. A single right or left coronary artery was found by Dabizzi et al.[30] in 4% of their series. They also noted origin of the anterior descending artery arising from the right coronary in 4% and large conal branches from the right coronary in 19%. The importance of these anomalous vessels is dependent on their course across the infundibulum. They may seriously interfere with relief of the right ventricular outflow tract obstruction at the time of corrective surgery. Damage to these coronary artery branches can result in myocardial infarction and death.[21] Small fistulous connections to the pulmonary artery or right atrium (11.7%), and anastomoses with the bronchial arteries (26%) were a surprisingly frequent finding by Dabizzi et al.[30] Rare cases of origin of the anterior descending from the internal mammary artery have also been reported.[32]

Most anomalies of the coronary arteries are identifiable by the surgeon at the time of repair. However, these vessels may be buried in the myocardium[33] or in adhesions from previous operations,[34] hence the importance of preoperative diagnosis. In most centers coronary artery anatomy is assessed from aortic root angiography. There are authors that recommend selective coronary arteriography in every patient.[30,31,35]

Lungs and Intrapulmonary Arteries

Quantitative studies have demonstrated a decrease in lung volume in patients with tetralogy of Fallot and tetralogy with pulmonary atresia.[15,36] The branching patterns of the bronchi, pulmonary arteries, and veins were normal. However, the total number of alveoli was reduced. The number of preacinar and intraacinar pulmonary arteries are also normal, but their size is smaller than normal.[15,36,37] All these changes have been attributed to low pulmonary blood flow. However, surgically created shunts may lead to dilatation of the proximal arteries without affecting the size of the intra-acinar vessels.[15] Since most of the alveolar and pulmonary artery growth is completed by two years of age, it has been suggested that repair by this age may result in normal alveolar development and growth of the pulmonary vascular bed.[15,37]

Associated Anomalies

Tetralogy of Fallot is frequently associated with other anomalies. A patent foramen ovale and an atrial septal defect are common. The incidence of interatrial communications has been reported as high as 82%.[6] Drainage of the left superior vena cava to the coronary sinus was found in 11% of cases in an autopsy series.[6] Rarely, the left superior vena cava may drain directly into the left atrium. Abnormal pulmonary venous corrections are very rare.[38] Other rare anomalies associated with tetralogy of Fallot include supravalvular mitral stenosis[39] and discrete subaortic stenosis.

Congenital anomalies of the aortic valve are extremely rare.[40] Aortic insufficiency is more common in adults with tetralogy of Fallot.[41] It is usually the result of bacterial endocarditis of the aortic valve, long-standing aortic root dilatation, or operative damage.[42]

Approximately 25% of patients with tetralogy of Fallot have a right-sided aortic arch. This bears surgical importance at the time of deciding between a classic or a modified Blalock-Taussig shunt (see section on Systemic to Pulmonary Artery Anastomoses).

EMBRYOLOGY

A brief review of the development of the normal heart assists in understanding the currently accepted hypothesis of the morphogenesis of the tetralogy of Fallot. The distal bulbus and the truncus lie above the developing right ventricle. This region is separated into aortic and pulmonary outflow tracts by growth and fusion of the bulbotruncal ridges. During this process there is rotation of the distal bulbus, which brings the aortic component posteriorly. The semilunar valves are developing at the bulbotruncal junction and are separated from the atrioventricular valves by the inner curvature of the heart (ventriculoinfundibular fold). Attenuation of a portion of the inner curvature will result in fibrous continuity between the mitral and aortic valves. As a consequence of this whole process the posterior outlet of the bulbotruncal region is transferred to the left ventricle. The infundibular septum is aligned with the trabecular septum, only separated by the interventricular foramen. This area will be eventually closed by endocardial cushion and sulcus tissue to form the membranous portion of the ventricular septum. The anterior outlet component remains connected to the right ventricle.[43]

Faulty rotation of the bulbotruncal region will result in incomplete transfer of the posterior component to the left ventricle. The infundibular septum will not be aligned with the developing trabecular septum resulting in a malalignment ventricular septal defect with aortic override. Attenuation of the inner curvature of the heart will still lead to continuity between the mitral and aortic valves. The tricuspid valve can also be expected to be in continuity with the aortic valve across the ventricular septal defect. Up to now, this process accounts for several of the morphologic features of the tetralogy of Fallot but is incapable of explaining the infundibular pulmonary stenosis. An abnormality in the separation of the distal bulbus is the postulated mechanism for this stenosis. Anterior displacement of the bulbotruncal ridges will result in unequal separation of the developing outflow tracts and lead to infundibular stenosis. The combination of the abnormal rotation of the bulbotruncal region with unequal separation of its components would explain the basic anatomic features of the tetralogy of Fallot.[44,45] The amount of aortic override will depend on the extent of the faulty rotation. Similarly, a wide range of severity of infundibular stenosis can be expected as a result of the degree of malseptation. These variations would account for the wide anatomic and clinical spectrum of this condition. Hypertrophy of the right ventricle is the hemodynamic result of the underlying morphology.

An alternative theory was postulated by Van Praagh et al. in 1970[25] who suggested that tetralogy of Fallot was the result of underdevelopment of the subpulmonary infundibulum. It was proposed that the hallmark of the tetralogy was an abnormally small infundibulum. The degree of right ventricular outflow obstruction

would be directly proportional to the amount of infundibular hypoplasia. This underdevelopment would also fail to align the distal conal (outlet) septum with the rest of the ventricular septum, therefore explaining the ventricular septal defect. As of yet, there is no experimental embryologic evidence to support this theory. Further anatomic studies have shown that a short subpulmonary infundibulum is not a constant feature of the tetralogy of Fallot. A morphometric study revealed that the infundibulum was actually longer than normal.[26]

The different portions of the normal pulmonary circulation have different embryologic origins. The main pulmonary artery originates from septation of the truncus arteriosus; the right and left pulmonary arteries and their confluence are most likely derived from the sixth aortic arch, while the intrapulmonary arteries develop with the airways from the primitive lung buds. In early embryonic life the intrapulmonary arteries are connected simultaneously to sixth aortic arch structures and to the descending aorta through the intersegmental arteries.[46,47] In pulmonary atresia with a ventricular septal defect, these intersegmental arteries persist as aortopulmonary collaterals.[13] These vessels are embryologically different from the bronchial arteries.[11]

EPIDEMIOLOGY AND GENETICS

Tetralogy of Fallot occurs in about 6% of infants born with congenital heart disease. The prevalence reported in any study is dependent upon the nature of the series and what group of patients was included or excluded from the numerator. In 1973, Campbell[48] summarized seven series describing the prevalence of different cardiac malformations at birth. The overall prevalence of tetralogy of Fallot was 5.8% with a range in each series from 3.5 to 8%. Hoffman and Christianson[49] evaluated congenital heart disease in a cohort of 19,502 births and reported a 3.7% prevalence of tetralogy of Fallot. When their data were combined with the data from six other series, tetralogy was found in 5.1% of over 300 infants with congenital heart disease. The prevalence reported in these other studies ranged from a low of 3.9% to a high of 8.6%. In the largest prospective survey, Mitchell et al.[50] found the prevalence of tetralogy of Fallot to be 3.5% of live births with congenital heart disease in a cohort of over 56,000 total births. In contrast, the prevalence of tetralogy of Fallot is reported to be higher in series of patients referred for evaluation of congenital heart disease. Some of these series include studies by Rowe (9.7%) in Toronto,[51] Kramer (10.4%) in West Germany,[52] and the New England Regional Infant Cardiac Program (11%).[53] Since these series include patients referred to medical centers for the diagnosis and treatment of cardiovascular malformations, it is possible that the denominator may not include patients with less severe abnormalities that were not referred for evaluation. Thus, the actual prevalence of tetralogy is difficult to determine exactly but probably lies in the range of about 6%.

The etiology of tetralogy of Fallot remains obscure. Although tetralogy and most other forms of congenital heart disease generally occur as isolated abnormalities, children with tetralogy of Fallot are afflicted with additional major extra cardiac malformations significantly more often (15.7%) as compared to patients with other congenital heart defects (6.8%).[52] In addition, the extracardiac malformations may be more serious in patients with tetralogy and include cleft lip and palate, hypospadius, and skeletal malformations. Although tetralogy is not commonly part of specific hereditary malformation syndromes or chromosomal anomalies, it is commonly found in a number of malformation associations including cardiofacial, VACTERL, and CHARGE associations as well as the de Lange, Goldenhar, and Klippel-Feil syndromes.[52,54,55] In general, tetralogy of Fallot appears to occur sporadically and is not familial. However, it has been found to occur in greater frequency in siblings of patients with tetralogy than would be expected to occur on the basis of its frequency in the general population.[55,56] Nora and Nora[55] also found a recurrence risk of 4% in offspring when one parent had tetralogy of Fallot. This was slightly higher than the 3% recurrence risk in siblings. This suggests a multifactorial inheritance resulting from a genetic–environmental interaction. In view of the absence of a familial incidence or genetic inheritance pattern for tetralogy of Fallot, it may be that some unknown environmental factor plays a major role in the production of this abnormality. Although no specific etiologic agent has been identified, potential environmental teratogenic agents include viral infections and drugs such as trimethadione, sex hormones, and thalidomide.[55] Of note is the fact that tetralogy of Fallot was not reported to have occurred in the offspring of a large group of mothers with congenital cardiac anomalies.[57] On the other hand, since large numbers of patients with tetralogy who were repaired in the 1960s are only now reaching child-bearing age, the true incidence of congenital heart defects in their offspring is still unknown.

PHYSIOLOGY AND HEMODYNAMICS

The hemodynamic features produced by the anatomic abnormalities in tetralogy of Fallot are 1) equalization of right and left ventricular pressure, and 2) normal or reduced pulmonary artery pressure. Since the ventricular septal defect is large and unrestrictive and the right and left ventricles contract simultaneously, the end result is in effect a ''common'' ventricular chamber ejecting into the systemic and pulmonary circulations. The pulmonary and systemic blood flows are therefore dependent upon the relationship between the pulmonary and systemic outflow resistances. Normally the pulmonary resistance is about 10% of the systemic resistance and these resistances are determined by the respective distal arteriolar beds. However, in tetralogy of Fallot, the pulmonary vascular (arteriolar) resistance is usually normal or less than normal and the total outflow resistance to right ventricular ejection into the pulmonary vascular bed is instead related to relatively fixed anatomic obstruction. Potential areas for anatomic obstruction include the right ventricular outflow tract at the subvalvar, annular, or valvar levels and supravalvar or distal arterial stenoses as well. Thus, in patients with tetralogy of Fallot, the resistance to systemic outflow is still the arteriolar resistance of the distal vascular bed while the resistance to pulmonary outflow is the cumulative effect of the various levels of outflow obstruction.[58] In a small number of patients, less than 5%, the ventricular septal defect may be partially obstructed by excess or accessory tricuspid valve tissue, which can result in suprasystemic right ventricular pressure.[23,24]

The presenting symptoms and severity of clinical manifestations in patients with tetralogy of Fallot are dependent upon the relationship between the resistances to systemic and pulmonary outflow as defined above.[59] If the total right ventricular ouflow ob-

struction is such that pulmonary outflow resistance is less than the systemic resistance, there will be a net left-to-right shunt and the clinical manifestations will be similar to those of patients with a small to moderate sized ventricular septal defect. If the pulmonary and systemic outflow resistances are similar, there will be a balanced shunt with nearly equal pulmonary and systemic blood flows at rest. Lastly, when the resistance to pulmonary ouflow exceeds systemic resistance, there will be a net right-to-left shunt and systemic flow will be greater than pulmonary flow. In tetralogy of Fallot with pulmonary atresia the pulmonary outflow resistance is, of course, at its maximal level. In these patients, pulmonary blood flow occurs by way of a patent ductus arteriosus, or systemic to pulmonary collateral vessels. In most cases, resistance to pulmonary blood flow is determined by the cross-sectional area of the vessel or vessels feeding into the pulmonary circulation. This is usually a fixed resistance and does not vary with alterations of the patient's physiologic state such as exercise. In some situations, the pulmonary blood flow is determined by the pulmonary arteriolar resistance rather than an anatomic obstruction. This occurs in patients with tetralogy of Fallot, or tetralogy of Fallot with pulmonary atresia, who have large unrestrictive systemic to pulmonary collateral vessels or who have a large surgically created systemic to pulmonary artery anastomosis. These patients usually have increased pulmonary blood flow, are acyanotic or mildly cyanotic at rest and may manifest congestive heart failure. Pulmonary hypertension is often present and if the large shunt persists over an extended period of time then pulmonary vascular disease may develop. This high degree of pulmonary blood flow and increased pulmonary to systemic flow ratio is very unusual in the large majority of patients with tetralogy of Fallot. Thus, congestive heart failure is extremely rare except in the situations that have just been described.

Cyanosis may be mild or undetectable at rest in patients with tetralogy of Fallot, but usually becomes apparent, or increases, with physical activity. This increase in right-to-left shunting and the resultant decrease in systemic arterial oxygen saturation can be explained on the basis of a number of physiologic alterations that occur with exercise. Although there normally is a considerable increase in cardiac output associated with exercise, there is also a fall in systemic and pulmonary vascular resistances so that only a modest increase in arterial pressure occurs. In the patient with tetralogy of Fallot, the total pulmonary outflow resistance is either fixed or the degree of right ventricular outflow obstruction may even increase as a result of increased myocardial contractility. Unchanged or increased pulmonary resistance associated with an increased cardiac output and decreased systemic arterial resistance results in a considerable increase in the degree of right-to-left shunting, while effective cardiac output is maintained. The rapid decrease in systemic arterial oxygen saturation produces exertional dyspnea and decreased exercise tolerance. In contrast to episodes of paroxysmal hypoxemia or "tetralogy spells" that are described below, the systemic desaturation is limited by the duration of exercise and begins to improve as soon as the activity ceases.

Squatting

Squatting is a common posture in patients with tetralogy of Fallot, particularly in young children. These children are usually not taught to do this but seem to learn instinctively that they are more comfortable when assuming this knee-chest position. Squatting is often seen in children after exercise. However, children frequently are seen to assume a squatting position while playing quiet games with their peers who are all in a sitting position. It is generally recognized that patients with tetralogy of Fallot assume the squatting position because they feel better as a result of increased systemic arterial oxygen saturation.[60] The exact mechanism by which this occurs is still unclear. It has been suggested by some that squatting is associated with a sustained decrease in systemic venous return from the lower extremities which, after exercise, reduces the proportion of this more highly desaturated blood returning to the heart.[61,62] It is more likely, however, that squatting results in an increase in systemic arterial resistance due to kinking and compression of the major arterial circulation to the lower extremities. This increase in peripheral resistance in the presence of the fixed pulmonary outflow resistance, decreases the degree of right-to-left shunting and increases the pulmonary blood flow. The result is an immediate increase in the systemic arterial oxygen saturation.

Paroxysmal Hypoxemic Spells

Episodes of paroxysmal hypoxemia, also called "hypercyanotic spells," "tetralogy spells," "paroxysmal dyspnea" and other synonyms, are commonly seen in infants and young children with tetralogy of Fallot and in other cardiac malformations with similar physiology (i.e., in which pulmonary blood flow is dependent upon the ratio of pulmonary to systemic resistance). This physiology may be present, for example, in tricuspid atresia, transposition, or Eisenmenger's syndrome. Hypoxemic spells are usually self-limited and of less than 15 to 30 minutes duration. However, there is considerable variability, and in any patient at any time, a spell may last only a few minutes or may last an hour or longer. The spells more commonly occur in the morning but may occur during the day, especially following a nap when systemic resistance is low. They may be precipitated by activity, a sudden fright, or injury, or may occur spontaneously without any apparent cause.[63] When a spell begins in an infant or a child after exercise or a fright, it is characterized by increasing cyanosis and an increased rate and depth of respiration. The small infant may initially just appear to be fussy but cannot be quieted and then progresses to have increased cyanosis and the respiratory features of a spell. Further discussion of the clinical manifestations and treatment of hypoxemic spells is found in the section on Management.

The physiologic change that produces a hypoxemic spell is an increase in right-to-left shunting and the concomitant decrease in pulmonary blood flow. Although this is the same mechanism that produces the decrease in systemic arterial oxygen saturation during exercise, the spell tends to be progressive and rapidly results in metabolic acidosis as compared to the reversal of desaturation that occurs when exercise ceases. Wood suggested that hypoxemic spells were due to spasm of the infundibulum of the right ventricle, which precipitated a cycle of progressively increasing right-to-left shunting and metabolic acidosis.[64] Others have postulated that an increase in circulating catecholamines and the resulting increase in myocardial contractility produces an increase in the degree of infundibular stenosis.[65] Although this is the most widely accepted explanation for paroxysmal hypoxemic spells, it does not explain spells that occur in patients with tetralogy of Fallot and pulmonary atresia or other similar malformations where pulmonary blood flow does not cross the right ventricular outflow tract. Guntheroth et

al. have suggested that episodes of paroxysmal hyperpnea are the cause rather than the effect of the hypoxemic spell.[66] They suggested that the hyperpnea augments systemic venous return thus increasing right-to-left shunting as well as oxygen consumption through the increased work of breathing. This results in further hypoxemia, decreased systemic vascular resistance, and a further increase in right-to-left shunting. Others have demonstrated an increase in right-to-left shunting associated with episodes of paroxysmal atrial tachycardia and during rapid atrial pacing,[67] implying that tachycardia with a decreased right ventricular volume may contribute to increased right-to-left shunting. Regardless of whether any or all of these mechanisms is responsible for hypoxemic spells, the clinical manifestations and course of these episodes would be similar. An increase in right-to-left shunt and decrease in pulmonary blood flow would result in reduction of the systolic murmur across the right ventricular outflow tract, an increase in cyanosis and the other characteristic features of a spell regardless of which came first.

CLINICAL FEATURES

The presentation of patients with tetralogy of Fallot is quite variable and ranges from the small infant with severe hypoxemia to the asymptomatic child with so called "pink tetralogy."[59] The severity of symptoms is related to the degree of pulmonary stenosis while the constancy of these symptoms is determined by whether the stenosis is fixed or is a dynamic phenomenon with episodic increases in severity. Cyanosis is noted most often in the neonate with associated pulmonary atresia. Cyanosis may be the only indication of the underlying abnormality since these patients often have no murmur, and a single second heart sound on auscultation is a common finding in a neonate. Another relatively common presentation is the asymptomatic infant with a heart murmur. These patients may seem to have only a ventricular septal defect, since the murmur of the right ventricular outflow tract obstruction in the infant with tetralogy may be indistinguishable from that of an isolated ventricular septal defect. Since the radiographic examination may be normal, the only clues to the presence of tetralogy may be the absence or splitting of the second heart sound and the presence of right ventricular hypertrophy on the electrocardiogram. However, sometimes it is difficult to appreciate splitting of the second heart sound in the small infant, especially in the presence of tachycardia and a loud murmur of a ventricular septal defect. In addition, since a degree of right ventricular hypertrophy on the electrocardiogram may be normal in the newborn and small infant, the significance of this finding may not be apparent until after 6 months of age. Fortunately, the diagnosis is easily made by echocardiography, which would be performed to evaluate a patient presenting with these findings. Typically, in tetralogy of Fallot, cyanosis is first noted at 6 weeks to 6 months of age.

When cyanosis is present in the patient with tetralogy of Fallot, it is usually apparent in the mucous membranes of the mouth and in the nailbeds. Cyanosis may be present at birth or may appear later during infancy or childhood as a result of progression of the pulmonary stenosis. Other patients with tetralogy may be acyanotic at rest, with cyanosis appearing only with exercise or during hypoxemic episodes. In patients with persistent cyanosis, clubbing of the fingers and toes generally appears during infancy (rarely before 6 months) and will persist until after complete repair. Since tetralogy of Fallot and ventricular septal defect are the most common associations with other major extracardiac anomalies, it is important to evaluate for these cardiac defects carefully when a murmur is found in a patient with extracardiac malformations.

The physical findings in patients with tetralogy of Fallot are not specific for this lesion and are also present in patients with other cardiac malformations. No abnormalities are usually found on inspection other than the cyanosis and clubbing previously mentioned. A prominent parasternal impulse may be present on palpation of the precordium but this is not a consistent finding. Although significant right ventricular hypertrophy is always present, there is no right ventricular volume overload and thus an abnormal right ventricular impulse may not be apparent.

On auscultation, the first heart sound is normal and the second heart sound is usually single. In some patients with tetralogy who are acyanotic, the infundibular pulmonary stenosis may be less severe and the pulmonary artery pressure may be normal rather than low. In these patients it may be possible to appreciate the pulmonic component of a second heart sound.[68] An ejection sound may sometimes be present at the mid to upper left sternal border. This is rarely a pulmonary ejection sound in patients who have valvular stenosis and less severe infundibular stenosis. In most cases, especially when there is pulmonary atresia, the ejection sound appears to arise from the aortic root and would be termed an aortic root click.[68,69]

It has been well established that the murmur in patients with tetralogy of Fallot is caused by the flow across the right ventricular outflow tract.[70] In patients with other types of stenotic lesions such as isolated pulmonary stenosis or even with isolated ventricular septal defect, the intensity of the murmur is directly related to the pressure gradient across the stenotic area. Thus, more severe degrees of valvar pulmonary stenosis and smaller ventricular septal defects are associated with louder murmurs. In contrast, in patients with tetralogy of Fallot or in those with similar physiology, the intensity of the murmur varies inversely with the degree of pulmonary stenosis. In tetralogy, as the degree of pulmonary stenosis increases, there is increased right-to-left shunting and decreased flow across the right ventricular outflow tract. The murmur therefore decreases as the degree of pulmonary stenosis increases. The murmur in patients with tetralogy of Fallot is characteristically an ejection or crescendo–decrescendo murmur and is usually loudest at the upper left sternal border. Despite the fact that this murmur is due to the pulmonary stenosis it is not unusual in infants to find a plateau-shaped pansystolic murmur that may even be best heard at the mid to low left sternal border.[68] Diastolic murmurs are uncommon in the preoperative patient with tetralogy of Fallot. Although aortic regurgitation is of concern in the long-term evaluation of these patients, especially postoperatively, it is unusual during childhood. A to-and-fro murmur of pulmonary stenosis and pulmonary regurgitation is characteristic of the syndrome of tetralogy of Fallot with absent pulmonary valve and is discussed in Chapter 64. Continuous murmurs are also uncommon, but when found suggest the presence of severe tetralogy of Fallot or tetralogy of Fallot with pulmonary atresia and collateral circulation.[68] The presence of a continuous murmur heard only in the left infraclavicular area anteriorly would suggest a patent ductus arteriosus. If a similar murmur is heard to the right of the sternum, this should raise the possibility of an unusual right-sided patent ductus arteriosus or possibly even bilateral ducti. Although this situation is

more commonly seen in patients with complex forms of pulmonary atresia, the presence of this unusual clinical finding warrants careful investigation of systemic to pulmonary communications at the time of cardiac catheterization. The finding of continuous murmurs both anteriorly and posteriorly suggest the presence of systemic to pulmonary collaterals rather than a patent ductus arteriosus. This situation is more commonly encountered in patients with tetralogy of Fallot and pulmonary atresia who characteristically have no other murmur. If an additional ejection murmur is heard at the upper left sternal border, this suggests tetralogy of Fallot with at least some flow across the right ventricular outflow tract.

The physical findings in postoperative patients are dependent upon the presence of residual abnormalities. An ejection systolic murmur may be present at the upper left sternal border with its intensity in proportion to the degree of residual ouflow tract obstruction. When a pulmonary valvectomy or transannular right ventricular ouflow patch was required at the time of operation to relieve severe stenosis, the low-pitched decrescendo early diastolic murmur of pulmonary regurgitation may be found at the mid to low left sternal border. This must be differentiated from the high-pitched decrescendo diastolic murmur of aortic regurgitation that may be seen on longterm follow-up of patients with tetralogy of Fallot. A plateau pansystolic murmur at the low left sternal border is usually produced by a residual ventricular septal defect. This murmur needs to be differentiated from that of tricuspid regurgitation, which can occur as a result of injury to the tricuspid valve at the time of operation. Although these murmurs may be similar, the murmur of tricuspid regurgitation varies with respiration and if the degree of regurgitation is significant, there will be prominent "v waves" in the jugular venous pulses and possibly hepatic pulsations as well. Lastly, this must also be differentiated from mitral valve regurgitation, which is usually heard more laterally. Mitral regurgitation is uncommon but may occur in patients with severe left ventricular dysfunction especially if the dysfunction is due to myocardial infarction that occurred as a result of injury to a coronary artery at the time of operation.

NONINVASIVE STUDIES

Electrocardiogram

Right ventricular hypertrophy on the electrocardiogram is characteristic in patients with tetralogy of Fallot. In the neonate or small infant, right ventricular preponderance is present normally and it may not be until 3 to 4 months of age that one can be certain that the right ventricular hypertrophy on electrocardiogram is abnormal. After this age, right ventricular hypertrophy on the electrocardiogram in a patient with clinical findings suggestive of a ventricular septal defect should alert the physician that tetralogy of Fallot may be present and indicate the necessity for echocardiographic evaluation. In general, right axis deviation is also found and the degree of this axis deviation corresponds to the severity of the right ventricular hypertrophy. Left axis deviation is found in a small percentage of cases and may indicate the presence of an atrioventricular septal defect with tetralogy of Fallot or may be a normal variant.[71] Sometimes the axis may be indeterminate, but with Q waves in leads I and AVL and without Q waves in leads II, III, and AVF. This indicates an initially counterclockwise frontal plane vector loop even though the classic pattern of left axis deviation is not present. It is important to recognize this pattern preoperatively since the shift to postoperative left axis deviation suggests bifascicular block which may represent operative damage to the cardiac conduction system.[72,73] Clearly, the recognition of a disguised form of left axis deviation preoperatively would make it apparent that this postoperative finding represented no change and had little significance.

Arrhythmias are uncommon in patients with tetralogy of Fallot before surgery. Complete AV block has been reported in up to 5% of postoperative patients and usually is an indication for implantation of a permanent pacemaker.[74] It was originally thought that late onset of complete heart block was responsible for the sudden death that occurs on late followup of patients who have had repair of tetralogy of Fallot.[74,75] Over the last decade, it has become increasingly recognized that this sudden death may be caused more commonly by ventricular arrhythmias rather than the late onset of complete heart block.[76,77] Thus, the presence of ventricular ectopy on a routine electrocardiogram indicates the need for further evaluation by stress exercise testing and 24-hour ambulatory electrocardiographic monitoring. The problem of ventricular arrhythmias is discussed further in the section on Late Results.

Radiography

The chest radiograph in older children with tetralogy of Fallot exhibits the classically described "boot shaped" heart or "coeur en sabot" (Fig. 63–7). This is caused by mild enlargement of the right ventricle and concavity of the upper left heart border caused by absence of the main pulmonary artery segment. This is accompanied by decreased pulmonary vascular markings resulting from the reduced pulmonary blood flow. Occasionally, patients with tetralogy of Fallot or, in particular, those with pulmonary atresia may have normal or increased pulmonary vascular markings. This is associated with the presence of systemic to pulmonary collat-

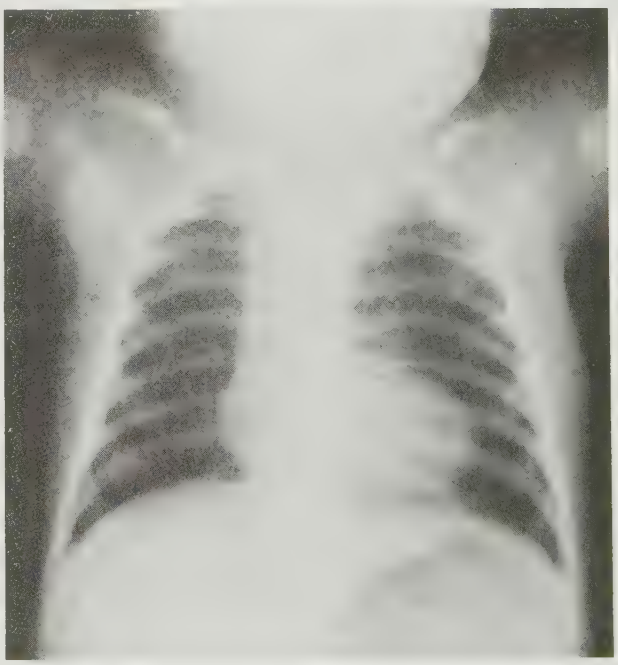

Fig. 63–7. Chest roentgenogram in tetralogy of Fallot.

erals. The combination of normal or increased pulmonary vascular markings and cardiomegaly suggests large collaterals with high pulmonary blood flow and should raise concern about the possibility of pulmonary hypertension in these vessels.

A right aortic arch is found in about one-fourth of patients with tetralogy of Fallot. Although this abnormality has little functional significance, it is extremely important when a systemic to pulmonary artery anastomosis is contemplated. A standard Blalock-Taussig anastomosis is performed on the side opposite the aortic arch, while a modified shunt is performed on the same side as the aortic arch. In addition, although a descending aorta to left pulmonary artery (Potts) anastomosis is rarely performed today, this procedure would be contraindicated if the aortic arch is to the right, since the bronchus will be interposed between the aorta and pulmonary artery.

In patients who have undergone a systemic to pulmonary artery anastomosis, the chest roentgenogram may reflect the hemodynamic effect of this procedure. If the anastomosis is large, increased pulmonary vascular markings are often seen on the side of the anastomosis, the ascending aorta is enlarged and cardiomegaly may be present. In patients who have undergone complete repair, the radiographic appearance is dependent upon the type and degree of residual abnormalities. A normal chest roentgenogram may be found in patients who have not required a transannular outflow patch and who have little or no volume overload from pulmonary insufficiency or a residual ventricular septal defect. Patients with only a mild to moderate degree of residual pulmonary stenosis may usually also have a normal chest roentgenogram. Increased pulmonary vascular markings and cardiomegaly may be found in patients with a residual ventricular septal defect and greater than twice normal pulmonary blood flow. If a transannular right ventricular outflow patch was necessary, pulmonary regurgitation is always present postoperatively. Right ventricular dilatation is usually found and there may be some aneurysmal dilatation of the right ventricular outflow region giving rise to the "box shaped" heart seen on chest roentgenogram in most of these patients. This problem will be discussed further in the section on Surgical Management.

Echocardiography

The anatomic features of the tetralogy of Fallot are generally identifiable echocardiographically. Prior to the availability of two-dimensional echocardiography, M-mode echocardiography revealed several features that were consistent with the diagnosis of the tetralogy of Fallot. On M-mode, a cranial "sweep" from the left ventricular cavity demonstrated discontinuity between the interventricular septum and the anterior wall of the aorta. This is due to the malalignment ventricular septal defect and overriding of the aortic root. Continuity between the anterior leaflet of the mitral valve and the posterior wall of the aorta is also demonstrated[78,79] (Fig. 63–8). These features are not exclusive of the tetralogy of Fallot and can be seen in other conditions with a malalignment ventricular septal defect. It can be very difficult to visualize the pulmonary valve using M-mode echocardiography alone.

The morphologic features of the tetralogy of Fallot are accurately identified by two-dimensional echocardiography. A systematized sequential approach allows visualization of the underlying anatomy from different positions as well as the associated anomalies.

From the parasternal long axis view the aorta overriding the ventricular septum is readily apparent (Fig. 63–9). The degree of override is best judged from this position.[80] More than 50% override could be considered a variant of double outlet right ventricle. The aortic root appears enlarged and there is fibrous continuity between the mitral valve and the aortic valve. After surgical correction, the patch closing the ventricular septal defect is clearly profiled. This view alone is not sufficient to diagnose the tetralogy of Fallot. Other conditions with a malalignment ventricular septal defect will share the above features.

Gentle clockwise and cranial angulation of the transducer will image the right ventricular outflow tract. Information on the severity of infundibular stenosis, pulmonary valve abnormalities and the main pulmonary artery can be obtained.

Further clockwise rotation will produce a short axis view at the level of the aortic root. If the ventricular septal defect is perimembranous it is possible to demonstrate tricuspid valve to aortic valve continuity across the defect. The cranial and anterior displacement of the outlet septum is visualized (Fig. 63–10) as well as the pulmonary valve, main, and branch pulmonary arteries.[81] It is important to demonstrate continuity between the right and left pulmonary artery since in tetralogy of Fallot, the right and left pulmonary artery may arise separately from the aorta. Continuous pulmonary arteries are best imaged from a high short axis position or from the suprasternal notch (Fig. 63–11). The presence of a patent ductus arteriosus as well as postoperative information on conduits used for reconstruction of the right ventricular outflow tract may be obtained from the short axis position.

Caudal angulation of the transducer will produce a short axis image of both ventricles. The right ventricle will appear hypertrophied and may also be dilated.

From the apex, a four chamber image will outline the anatomy of the crux of the heart. Straddling of the mitral or tricuspid valves can be identified as well as the rare association of a complete atrioventricular septal defect with tetralogy of Fallot. Occasionally there is a persistent left superior vena cava draining to the coronary sinus. When present, the coronary sinus is usually dilated. Abnormalities of pulmonary venous connections are rare, but should be excluded. Careful scanning along the ventricular septum will reveal the presence of additional ventricular septal defects. Cranial angulation of the transducer will outline the left ventricular outflow tract and the malalignment ventricular septal defect. There will be fibrous continuity between the tricuspid and aortic valves if the defect is perimembranous. If the defect is muscular, there will be a muscle bar separating the tricuspid and aortic valves. Following surgical correction, the patch closing the ventricular septal defect is imaged as a bright echogenic structure.

Abnormalities of pulmonary and systemic venous return can be demonstrated from the subcostal position. This also is the best view for diagnosing atrial septal defects that are commonly associated with tetralogy of Fallot. From a subcostal four chamber view, cranial angulation and clockwise rotation of the transducer will demonstrate the overriding aortic root and the ventricular septal defect (Fig. 63–12A). Counterclockwise rotation will show the right ventricle with its inlet, trabecular, and outlet portions. The anterior deviation of the outlet septum producing infundibular stenosis is best visualized from this image (Fig. 63–12B).[82–84] The

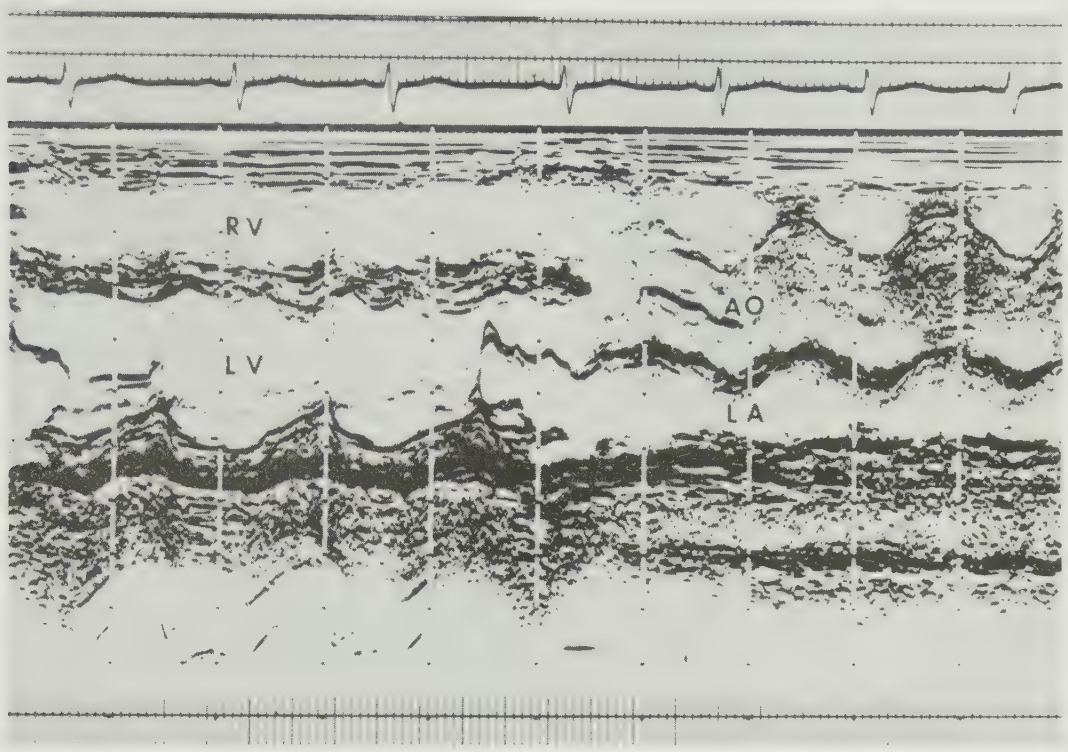

Fig. 63–8. M-mode echocardiogram in tetralogy of Fallot.

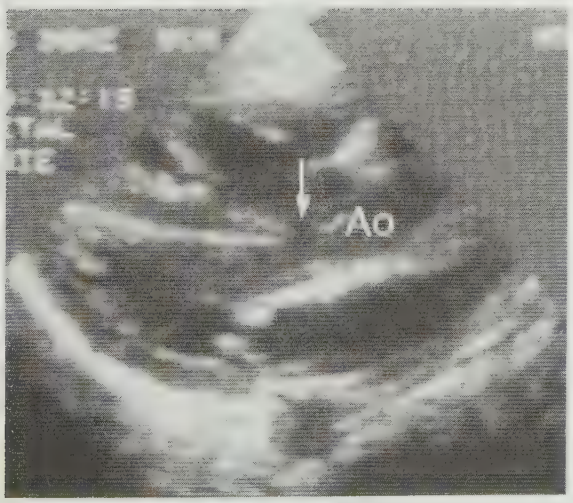

Fig. 63–9. Cross-sectional echocardiogram in the long axis view in tetralogy of Fallot demonstrating the bi-ventricular origin of the aorta with a large ventricular septal defect (arrow).

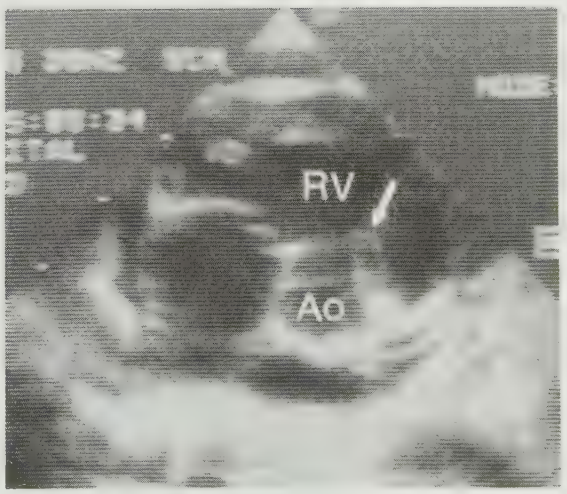

Fig. 63–10. Parasternal short axis echocardiogram in tetralogy of Fallot demonstrating the deviation of the outlet septum (arrow).

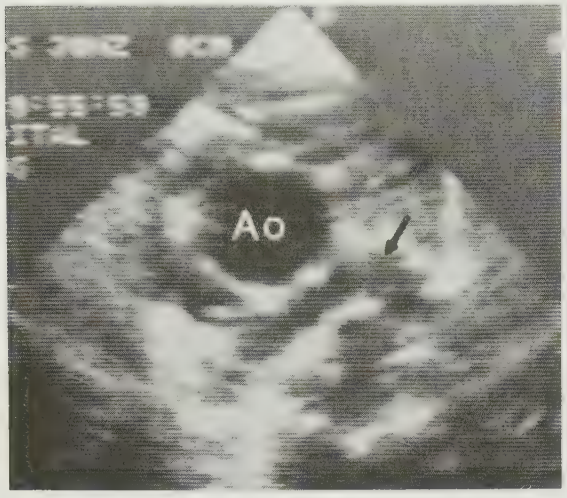

Fig. 63–11. High parasternal short axis echocardiogram demonstrating continuous pulmonary arteries (arrow).

pulmonary valve, main pulmonary artery, and proximal portions of the right and left branches (particularly in neonates and infants) are also seen.

Determination of the side of the aortic arch is very important, particularly if an infant is being referred for palliative surgery on the sole basis of noninvasive investigations. Approximately 25% of patients with tetralogy of Fallot have a right aortic arch. A left aortic arch is fully imaged from the suprasternal notch with the plane of the transducer aimed toward the angle of the left scapula. Visualization of the bifurcation of the first arch vessel will show a right brachiocephalic artery. A right aortic arch is only partially imaged from the standard position. Counterclockwise rotation of the transducer with the imaging plane toward the right will then profile the arch, the first vessel being a left brachiocephalic artery. From the suprasternal notch the right pulmonary artery is imaged below the aortic arch. Clockwise rotation of the transducer will demonstrate continuity between the right and left pulmonary artery if it is present. Growth of small pulmonary arteries can be serially assessed.

Doppler echocardiography adds hemodynamic information to the anatomical findings obtained from the cross-sectional scan. The presence of a patent ductus arteriosus as well as incompetence of the mitral and tricuspid valves is readily identified. Flow across the atrial septum can be accurately detected by color flow mapping. Color Doppler is also useful for the detection of multiple ventricular septal defects. It is possible to estimate the gradient across the right ventricular ouflow tract and systemic to pulmonary artery shunts using continuous wave Doppler.

After surgical correction of the tetralogy of Fallot, pulmonary insufficiency and residual right ventricular outflow tract obstruction are common. The severity of these hemodynamic sequelae are amenable to evaluation with Doppler techniques. After conduit reconstruction of the right ventricular outflow tract, serial Doppler studies allow detection of conduit obstruction as well as followup of the progression. The presence of residual ventricular septal defects can also be established.

In patients with tetralogy of Fallot and pulmonary atresia, the echocardiographic features are very similar except those regarding the right ventricular outflow tract and the pulmonary arteries. Atresia may occur at infundibular, valve, or pulmonary artery level. Careful scanning of the right ventricular ouflow tract from the parasternal and subcostal positions is warranted for identification of the atretic site. A blind ending infundibulum can be demonstrated, especially with combined cross-sectional echocardiography and Doppler evaluation. It is important to establish whether a main pulmonary artery is present and if there is continuity between the right and left branch pulmonary arteries.[85,86] Echocar-

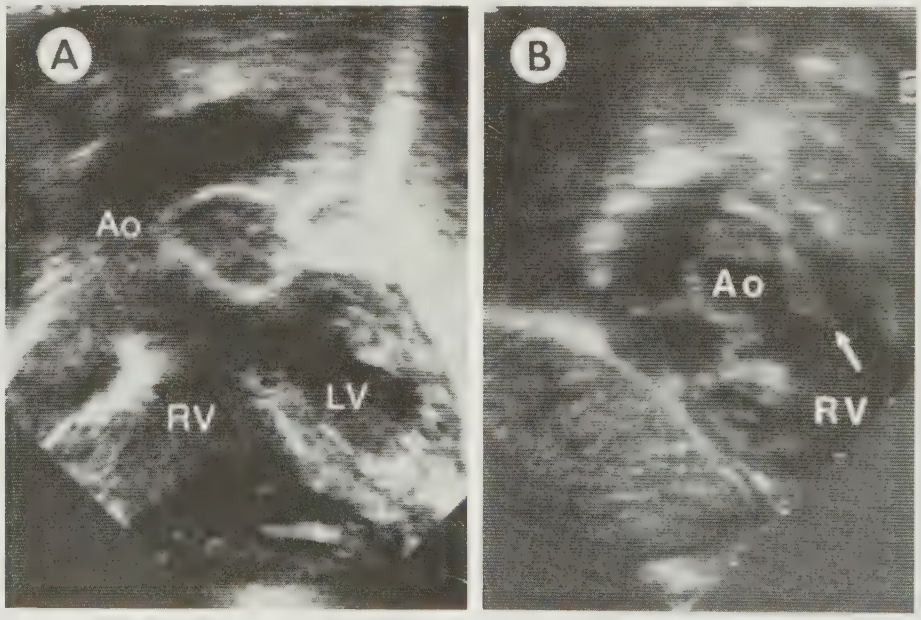

Fig. 63–12. Subcostal four chamber echocardiograms in tetralogy of Fallot. (A) Demonstrating the overriding aorta and large ventricular septal defect. (B) Demonstrating the area of infundibular pulmonary stenosis (arrow).

diographically it can be difficult to distinguish between true pulmonary arteries and major aortopulmonary collateral vessels. The latter may often be imaged from the suprasternal notch arising from the aorta. Unfortunately, it is not possible to follow their distribution within the lungs. Color flow mapping increases the accuracy of detection of aortopulmonary collaterals and the presence of proximal stenosis within them. In tetralogy of Fallot with pulmonary atresia, the aortic arch is often right sided.

Two-dimensional and Doppler echocardiography are invaluable noninvasive techniques. In combination they provide accurate anatomic and hemodynamic data for the diagnosis and longterm followup of patients with the tetralogy of Fallot.

CARDIAC CATHETERIZATION

The diagnosis of tetralogy of Fallot is usually suspected on the basis of clinical findings and can be readily confirmed by two-dimensional and Doppler echocardiography. Cardiac catheterization and angiocardiography are important in the evaluation of the patient with tetralogy of Fallot both preoperatively and postoperatively. In the preoperative patient it is important to define the levels of stenosis in the right ventricular outflow tract and pulmonary artery[87,88] and hopefully to predict accurately whether the repair is likely to be successfully accomplished.[89–91] It is extremely important to demonstrate features such as multiple ventricular septal defects or coronary artery anomalies that might have an adverse affect on the success of surgical repair.[35,88,92] The assessment of hemodynamic result and ventricular function, residual anatomic abnormalities, and electrophysiologic studies is important in the evaluation and followup of patients postoperatively.[93–97]

Catheterization Prior to Complete Repair

A standard protocol is followed for hemodynamics and oximetry while the sites of injection and views for angiocardiography are selected to define the anatomy and associated abnormalities in tetralogy of Fallot. Catheters are usually inserted into the femoral vessels and entry into the pulmonary artery is most difficult from this position. Since crossing the right ventricular outflow tract with the catheter is sometimes associated with a hypoxemic spell, we recommend measurement of oxygen consumption and assessment of hemodynamics and oximetry at all other sites prior to attempts at crossing the right ventricular outflow tract with the catheter. In this way, even if a hypoxemic spell is induced, baseline measurements will have been obtained beforehand. In many laboratories, flow-directed balloon catheters are used for right heart procedures. In patients with tetralogy of Fallot with moderate to severe pulmonary stenosis, the right-to-left shunt will result in a flow-directed balloon catheter passing from the right ventricle into the aorta. In these patients, entry into the pulmonary artery, if desired, may be only possible with a woven Dacron or some other type of nonflow-directed catheter. It is usually possible to enter the left heart and the aorta with the venous catheter in patients with tetralogy of Fallot. Since an atrial communication, either a patent foramen ovale or atrial septal defect is commonly present, the venous catheter can be advanced across the atrial septal communication into the left atrium and from there into the left ventricle. It is also frequently possible to manipulate the catheter from the right ventricle out into the aorta. In many cases, where the atrial septum is intact and the catheter has been advanced into the aorta, it is possible to manipulate this catheter into the left ventricle across the ventricular septal defect. This is accomplished by maintaining counterclockwise twist on the catheter as it is withdrawn from the ascending aorta into the ventricle. This counterclockwise twist will result in the catheter tip flipping into the left ventricle rather than the right ventricle as it is withdrawn from the aorta.

Oxygen saturations are determined at standard sites within the cardiovascular system and the data used for calculation of pulmonary and systemic blood flow. If oxygen consumption is measured, then actual pulmonary and systemic blood flows can be calculated. Otherwise, the pulmonary to systemic flow ratio can be used. Although some patients have a balanced shunt or net left-to-right shunt, most patients with tetralogy of Fallot have a net right-to-left shunt and at least some degree of systemic arterial desaturation. The degree of right-to-left shunting can be quantified either by oximetry or by means of indicator dilution curves.

The ventricular septal defect is unrestrictive in patients with tetralogy of Fallot and thus the systolic pressures are the same in both ventricles and the aorta. If the systolic pressure is the same in the left ventricle and the aorta and higher than that in the right ventricle (and this is not an artifact of measurement), then the ventricular septal defect is somewhat restrictive and the right ventricle does not freely communicate with the aorta. Even though infundibular pulmonary stenosis is present, this raises the question as to whether or not the patient truly has tetralogy of Fallot. If the systolic pressure in the right ventricle and aorta are the same and the left ventricle pressure is higher, the possibility of double outlet right ventricle with a restrictive interventricular communication must be considered. In the rare case of tetralogy with suprasystemic right ventricular pressure, partial occlusion of the ventricular septal defect by excess, or accessory tricuspid valve tissue will be demonstrated angiographically.

If it is possible to pass a catheter into the pulmonary artery, the slow withdrawal of an end-hole catheter from the distal pulmonary arteries to the right ventricle may demonstrate additional sites of stenosis in the distal pulmonary artery, in the supravalvar region, or at the valvar level. However, the proximal infundibular stenosis and right-to-left shunt at ventricular level will make the pressure gradient across more distal areas of stenosis an unreliable measure of their severity. This is best assessed by angiocardiography. It is important to measure the pulmonary artery pressure in patients who are being considered for corrective surgery and who previously had a systemic to pulmonary artery anastomosis. This is especially true if the patient has had a Waterston, Potts, or other central shunt. Pulmonary hypertension may occur in patients who have undergone these palliative surgical procedures and if present, may be a serious complicating factor at the time of complete repair.[98,99]

Angiocardiography

Angiocardiography complements the information obtained by echocardiography and is a valuable tool for the assessment of the anatomic severity of tetralogy of Fallot and the demonstration of the nature and severity of associated abnormalities. These include definition of the levels of obstruction to right ventricular outflow, anatomy of the pulmonary arteries, and the presence of multiple ventricular septal defects or coronary artery anomalies. Stenosis in the right ventricular outflow tract is demonstrated by a selective injection in the right ventricle.[87,88,92] If movable "C-Arm" equip-

ment is available, right anterior oblique and lateral views can be used. Otherwise, with fixed bi-plane equipment, right and left anterior oblique, or anteroposterior and lateral views will demonstrate the anatomy (Fig. 63–13). To best visualize the pulmonary arteries, a combination of compound axial views, described by Bargeron et al.,[100] is used. An anteroposterior projection with about 30° of craniocaudal angulation (''sitting up'' view) will visualize the main pulmonary artery, pulmonary artery bifurcation and pulmonary artery branches (Fig. 63–14).[88,101] The left pulmonary artery is best seen if the lateral camera can be used to obtain a four-chamber view (left anterior oblique with craniocaudal angulation). It is often helpful to visualize the right ventricular outflow tract and pulmonary artery simultaneously, especially when it has not been possible to enter the pulmonary artery with the catheter. This is accomplished by a hand injection of contrast in the right ventricular outflow tract using an end-hole catheter (Lehman or Goodale) and in the compound views that have been just described.

A selective injection of contrast material in the left ventricle will demonstrate left ventricular anatomy, function, and the defect in the interventricular septum. This is best performed in the left anterior oblique view with craniocaudal angulation (four chamber or long axial oblique view) and with a complementary right anterior oblique or separate anteroposterior projection depending upon the kind of equipment that is available. The four chamber or long axial oblique projection will demonstrate the ventricular septal defect in the left ventricular outflow tract and will nicely profile the trabecular portion of the interventricular septum to evaluate for the presence of multiple or muscular ventricular septal defects.[88] Mitral-aortic valve continuity is demonstrated on the lateral view of the left ventricular injection and should be evaluated if double outlet right ventricle is suspected on the basis of other parameters or echocardiography.

Opacification of the aorta (visualized from either a ventricular injection or an ascending aortic injection) is important to document the side of the aortic arch and the anatomy of the brachiocephalic vessels. This information is important for the surgeon if a patient is to undergo a systemic to pulmonary artery anastomosis. In preparation for complete repair, it is important to determine if a patent ductus arteriosus or large systemic to pulmonary artery collaterals are present, since these vessels should be ligated at the time of operation. Lastly, the coronary artery pattern must be demonstrated in the patient who is to undergo complete repair.[88,102] Coronary artery anomalies such as an accessory anterior descending, or an anterior descending coronary artery arising from the right coronary artery, have great importance at the time of surgical repair.[34,35] In both of these cases, the anterior descending coronary artery or the accessory branch arises from the right coronary artery and crosses the right ventricular outflow tract before it follows in the normal distribution (Fig. 63–15). The potential for damage to this vessel is extremely high with a standard right ventriculotomy incision for repair of tetralogy of Fallot. Knowledge of the existence of this anomaly will enable the surgeon to modify the operative technique thus hopefully avoiding damage to a major coronary artery supplying the interventricular septum and left ventricular myocardium. Since it is usually possible to pass the catheter from the right ventricle out into the aorta, an injection with this catheter may visualize the coronary artery anatomy and also evaluate for aortic regurgitation.[88,102] If the coronary arteries cannot be demonstrated adequately, then a selective injection in the ascending aorta with a retrograde catheter is necessary. If the coronary artery pattern still cannot be visualized adequately using an aortic root injection, then selective coronary arteriography should be performed.[30,35]

In patients with tetralogy of Fallot and pulmonary atresia, most commonly, pulmonary blood flow is by means of one or more

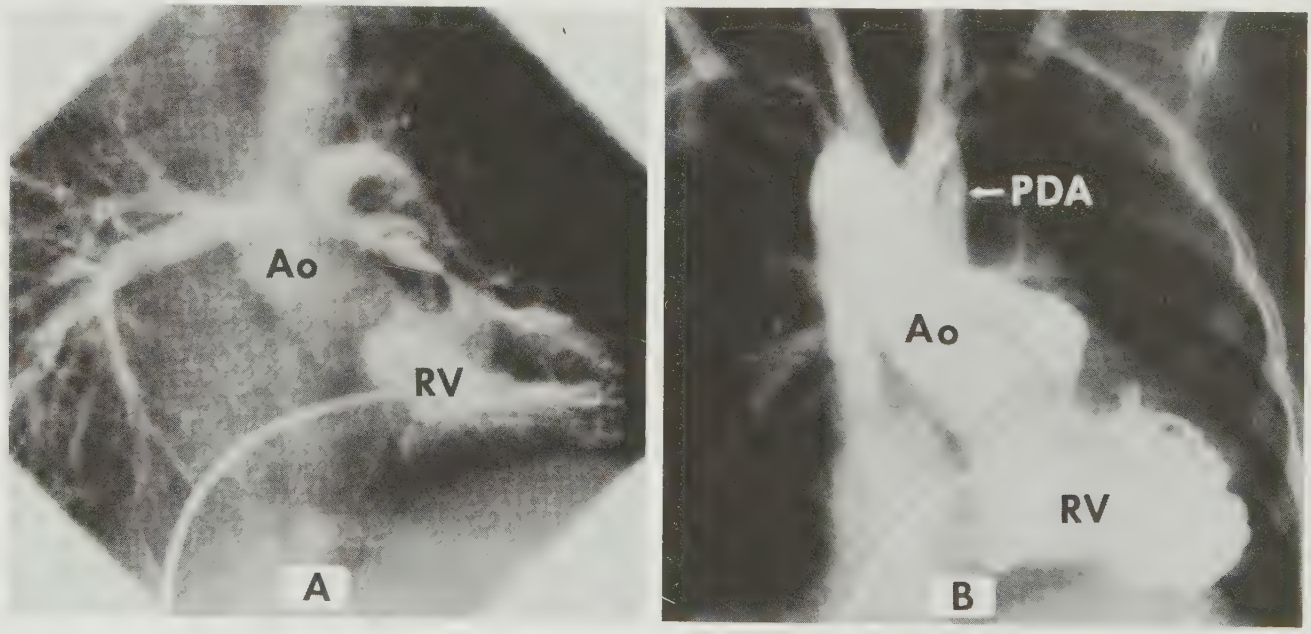

Fig. 63–13. Right ventricular angiocardiogram in tetralogy of Fallot. (A) Severe subpulmonary stenosis and a right to left shunt are demonstrated. The aortic arch is left sided. (B) Similar features as in part (A) but with a right aortic arch and left sided ductus arteriosus (PDA).

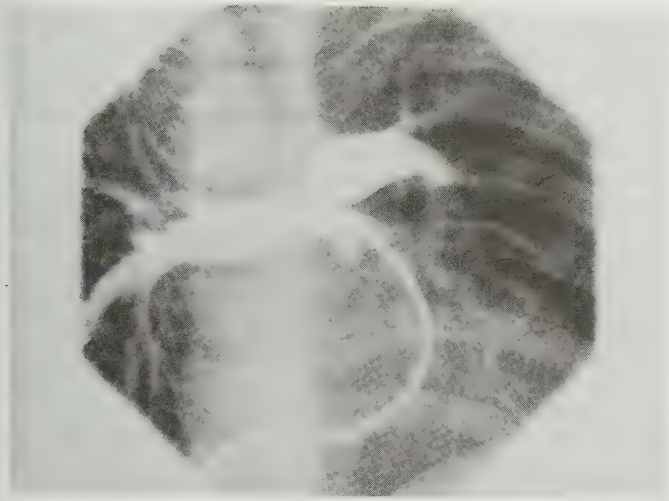

Fig. 63–14. Angiocardiogram demonstrating pulmonary artery anatomy (anteroposterior view with craniocaudal angulation, "sitting up" view).

large systemic to pulmonary collateral arteries arising from the descending thoracic aorta.[14,15,18,19,103,104] The pulmonary arteries are usually small and often are extremely hypoplastic. There are wide variations in the nature of the pulmonary blood supply (see Fig. 63–5). Collateral arteries may connect directly to a pulmonary artery and thus provide pulmonary blood flow to an entire lung. These vessels may also feed directly into a pulmonary segment resulting in either dual supply to that segment (from the collateral and from the true pulmonary artery), or may be the sole supply to that segment with the result that some portions of the lung are supplied by collaterals and other portions by a true pulmonary artery.[19,104] The precise anatomy and distribution of the pulmonary blood supply can be demonstrated angiographically. An injection of contrast in the descending thoracic aorta will serve as a screening procedure to define the number and position of systemic to pulmonary collateral arteries (Fig. 63–16). Subsequent selective injections in each of these collateral vessels are important to demonstrate the size and distribution as well as areas of stenosis in the collateral artery.[105] True pulmonary arteries are often still unidentified following the selective injections in the systemic to pulmonary collaterals. Pulmonary vein wedge angiography, which is described in detail in another chapter in this book, is often necessary to define the true pulmonary arterial artery.[106] Demonstration of the size, distribution, and continuity between right and left pulmonary arteries is important information in the surgical management of patients with tetralogy of Fallot and pulmonary atresia and will be discussed later in this chapter.

Other Catheterization Procedures—Preoperative or Postoperative

Electrophysiology

Most centers do not routinely perform intracardiac electrophysiologic studies postoperatively despite the fact that a significant incidence of atrioventricular conduction abnormalities have been reported following complete repair of this anomaly.[72–74] Neches et al.[107] and others[108] have reported that at least 25% of postoperative patients show abnormalities of atrioventricular conduction that were not present preoperatively. Electrophysiologic screening procedures are easily performed with a single catheter and may identify abnormalities that warrant further, more sophisticated evalu-

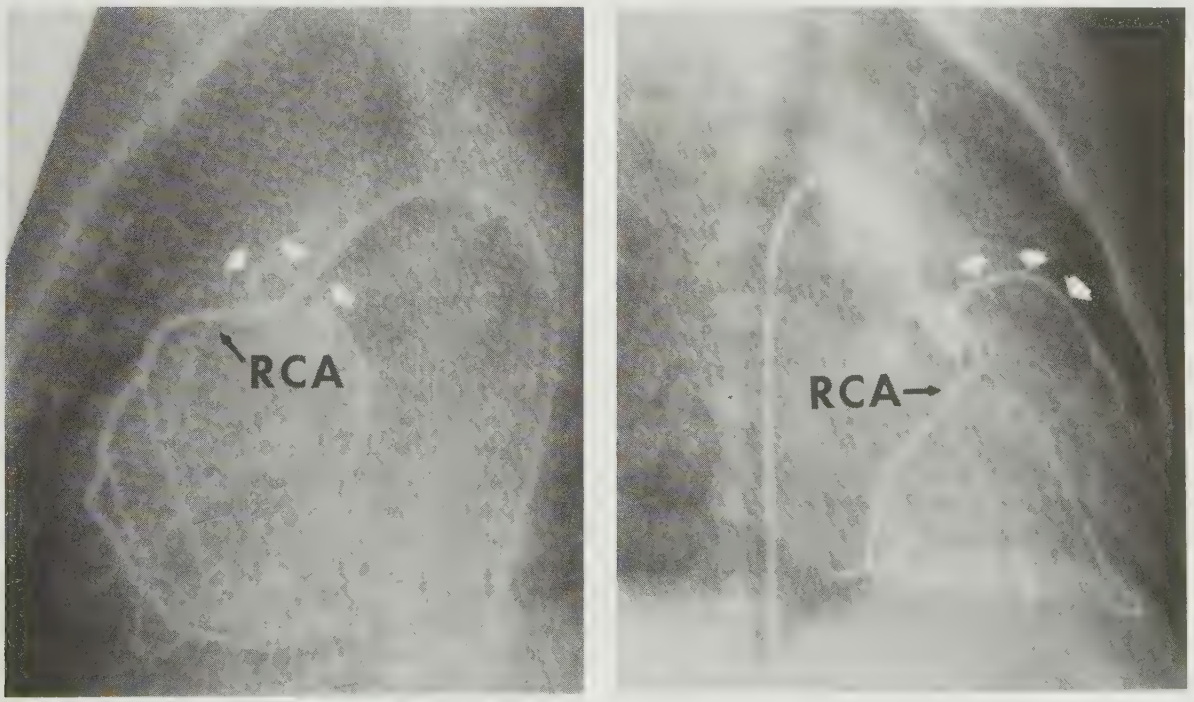

Fig. 63–15. Selective right coronary arteriogram demonstrating an anomalous anterior descending coronary artery (arrows) arising from the right coronary artery (RCA). Left = RAO projection; Right = LAO projection.

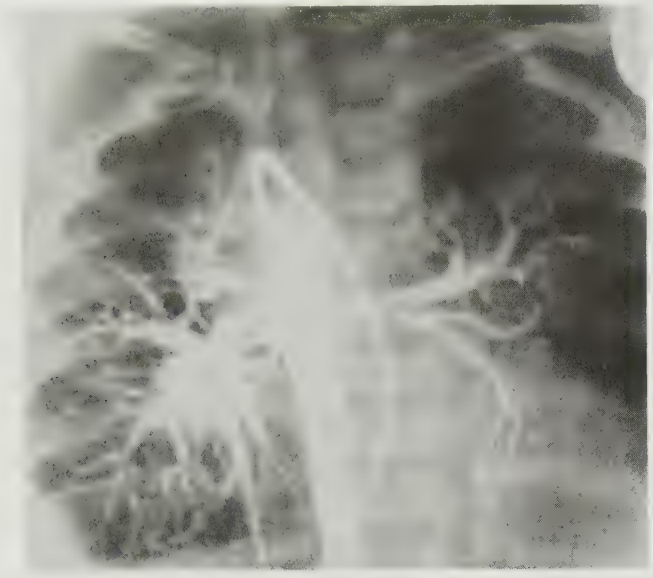

Fig. 63–16. Descending aortogram demonstrating aortopulmonary collateral arteries.

ation. The studies performed with a single catheter include obtaining a His bundle electrogram, measurement of resting AH and HV intervals, and incremental atrial pacing to determine AV node refractoriness and sinus node recovery time. Although the significance of the abnormalities that have been found in these patients is still unknown, the high incidence of abnormalities found in this group and not present in other groups of postoperative patients are bothersome and indicate a subgroup that may be at greater risk for problems in the future.

Ventricular arrhythmias may be found following repair of tetralogy of Fallot. It has been suggested that the finding of premature ventricular beats on resting or exercise electrocardiography may be a marker for those patients who may develop serious ventricular arrhythmias and sudden death.[76,77] An intracardiac electrophysiologic study would be indicated for those postoperative patients in a high risk category such as those with previous episodes of syncope or suspected arrhythmia, or to facilitate the selection of pharmacologic therapy in patients with serious and life-threatening arrhythmias.

Interventional Catheterization Procedures

Percutaneous balloon angioplasty has become widely used in management of coronary artery disease and valvar stenosis in adults and in a number of congenital cardiac abnormalities including valvar pulmonary stenosis, valvar aortic stenosis, and coarctation of the aorta.[109–111] This technique has been used in a few preoperative patients with tetralogy of Fallot[112] and successful balloon dilatation of a stenotic Blalock-Taussig systemic to pulmonary artery anastomosis has also been reported.[113] In addition, balloon dilatation of residual pulmonary artery stenosis in patients who have undergone complete repair of tetralogy of Fallot may be an important future application.[114] In the past, balloon dilatation of pulmonary artery stenosis usually has not been successful due to the inability to maintain the area of pulmonary artery stenosis in its dilated state after deflation and removal of the balloon dilatation catheter. A potentially valuable technique that is currently under investigation involves the use of a wire mesh stent that surrounds the surface of a deflated balloon dilatation catheter.[115] When this device is inserted into a stenotic area of pulmonary artery and the balloon inflated, the stent assumes a new and larger diameter. When the balloon is deflated the metal stent retains the enlarged diameter and thus prevents the surrounding stenotic area of pulmonary artery from returning to its previous size. This technique holds particular promise for the treatment of areas of distal pulmonary artery stenosis in patients who have undergone complete repair. These areas of stenosis are often at the site of distal anastomoses of the pulmonary artery with conduits or patches and are usually not amenable to further surgical intervention. Finally, coils may be used to occlude collateral vessels that persist after complete repair.

MEDICAL MANAGEMENT OF TETRALOGY OF FALLOT

Natural History

The presentation and clinical course of patients with tetralogy of Fallot depend on the degree of pulmonary stenosis. Although many patients are acyanotic in early infancy, the subpulmonary stenosis tends to be progressive and usually results in the appearance of cyanosis during infancy or early childhood. Prior to the development of systemic to pulmonary artery anastomoses in the mid 1940s, approximately 50% of patients with tetralogy of Fallot died in the first few years of life and it was unusual for a patient to survive past the third decade.[116,117] Mortality was usually either a direct consequence of hypoxia, secondary hematologic changes, or problems such as infectious endocarditis or brain abscess.[118,119] With the advent of palliative procedures and complete repair, which now is possible even during infancy and early childhood, 85% or more of patients with tetralogy of Fallot would be expected to survive to adulthood. These various surgical modalities that have had such a profound affect on the survival of patients with tetralogy of Fallot, as well as many other types of congenital heart disease, will be described in this section following a discussion of the medical management of the effects of hypoxia during infancy and childhood.

Hypoxia and Polycythemia

In patients with tetralogy of Fallot, the treatment of significant resting hypoxia and/or hypercyanotic spells is surgical. Since the mid 1940s, systemic to pulmonary artery anastomoses have generally provided adequate palliation and since the mid 1950s, corrective procedures have been possible. The resting systemic arterial oxygen saturation is quite variable in asymptomatic patients with tetralogy of Fallot and may be from the low 70s to the mid 90s depending upon the degree of pulmonary stenosis. Any type of physical activity, either feeding or crying in the infant or other exercise in a child, results in a fall in the systemic arterial oxygen saturation. Although these patients certainly have less exercise capacity and stamina than their normal and healthy siblings and peers, this systemic desaturation does not seem to have a great effect on growth and development in many cases. However, some investigators have found that patients with the tetralogy of Fallot have delayed growth or development as compared to their normal peers even when they have had adequate palliation.[120,121] Unfor-

tunately, it is extremely difficult to determine the specific etiology of these developmental problems. As was mentioned earlier in this chapter, many patients with tetralogy of Fallot have other associated congenital anomalies. In addition, although it is possible that growth and development problems are related to cyanosis, these patients also may undergo multiple cardiovascular procedures. Thus some of these problems may be related to the surgical procedures, to the timing of these procedures, or possibly even to the psychosocial abnormalities that are known to occur in this group of patients.[122–124]

Polycythemia is a major physiologic consequence of the presence of hypoxemia. In general, patients with tetralogy of Fallot and an adequate systemic oxygen saturation at rest, have an increased red blood cell count and a hemoglobin in the range between 15 and 17 g/dL. This corresponds to a hematocrit between 45 and 50%. When the hematocrit is in this range, the increased number of red blood cells is sufficient to provide adequate peripheral oxygen delivery while it is not so high as to produce the serious side effects of polycythemia. However, when the hematocrit is above 60%, the viscosity of blood increases geometrically for each increase in the percent hematocrit. This tends to provide a substantial increase in blood viscosity especially when the hematocrit is over 65%.[125] The increased viscosity results in peripheral sludging of blood and places the patient at greater risk for having the neurologic complications that will be described below. Another important complication of high hematocrit and high blood viscosity is the alteration of clotting factors that occurs in these patients.[126,127] When the hematocrit is 65% or higher, there is an alteration of the coagulation status with increased prothrombin time, low platelet count, decreased concentration of fibrinogen and other coagulation factors. This most likely occurs as a result of a subclinical consumption coagulopathy.[127,128] Although this altered coagulation state is usually of little consequence, it is a serious problem for the patient who is about to undergo open heart surgery. Thus, when a polycythemic patient with a hematocrit of over 60% is about to undergo complete surgical repair rather than a systemic to pulmonary artery shunt, it is important to check the patient's coagulation profile about a month prior to operation. If it is found to be abnormal, then phlebotomy and an exchange with a plasma substitute is performed in some centers approximately 1 week to 10 days prior to operation. Reduction of the hematocrit below 60% serves to improve the cardiovascular status,[129] reduce peripheral sludging, and will improve the patient's coagulation status, thus minimizing the risk of bleeding diathesis postoperatively.[130]

Neurologic Complications

Patients with tetralogy of Fallot, especially those with marked polycythemia, are at risk for a number of neurologic problems, some of which are readily reversible and others that have permanent residua.[119,120] Headaches are a common complaint of patients with polycythemia (especially when their hematocrit is over 65%) and these are probably related to the sludging of blood in the capillary circulation of the brain. These symptoms are usually relieved by the reduction or elimination of cyanosis and polycythemia that occurs as a result of palliative or corrective surgical procedures. If the systemic arterial oxygen saturation cannot be improved by surgical means, such as sometimes occurs in patients with tetralogy of Fallot and pulmonary atresia, the symptoms related to marked polycythemia are temporarily reversed following phlebotomy procedures. In these patients it may be necessary to perform routine phlebotomy and exchange transfusion with a plasma substitute in order to maintain the hematocrit in a range at which the patient will remain free of symptoms.

Delayed intellectual and/or motor development and seizures may occur in patients with tetralogy of Fallot.[118,121] It is possible that these problems are related to the systemic hypoxemia that many of these patients have during infancy.[122] However, it must be remembered that in patients with tetralogy of Fallot, as in other patients with cyanotic congenital heart disease, there is a direct route from the systemic venous circulation to the systemic arterial circulation and thereby to the brain. Spontaneous intravascular thromboses, either arterial or venous, can occur in the presence of severe polycythemia. Thus, small intracerebral vessel thrombosis or peripheral venous thrombosis with systemic arterial embolization, can occur in the absence of an apparent major clinical event and yet result in these neurologic abnormalities. In the same respect, these patients may have inadvertent systemic arterial embolization during one of their cardiac catheterizations or surgical procedures. Cerebrovascular accidents, which are more severe and permanent neurologic complications, may have the same underlying mechanism. These are often temporally related to procedures although as many as 50% can occur spontaneously.[118]

Although the majority of these complications are related to procedures or occur in polycythemic patients, anemia may also be a factor.[118,119] While a hemoglobin concentration of 12 to 14 g/dL is normal for a noncyanotic patient, this level of hemoglobin, or lower, represents a significant relative anemia for a patient with tetralogy of Fallot who is quite cyanotic. It has been our experience and that of others, that relative anemia in a cyanotic patient is as much a risk factor for a cerebrovascular accident as is severe polycythemia. Thus, patients with significant resting cyanosis and a hemoglobin at either extreme (with a hemoglobin below 15 grams or above 20 grams), are at risk for the development of neurologic complications especially during infectious illnesses. Careful attention must be paid not only to polycythemia but also to relative anemia. If a patient with tetralogy of Fallot and hypoxemia is found to have a hematocrit less than 15 g/dL, supplemental oral iron therapy should be instituted to raise the hemoglobin and hematocrit to what is considered to be an appropriate level for that patient's degree of cyanosis and hypoxemia.

Infection is another important cause of neurologic complications in patients with tetralogy of Fallot. As a result of the right-to-left shunt, there is a direct route from the systemic venous circulation into the systemic arterial circulation and to the brain. Thus, bacteremia that is produced by systemic infectious illnesses, or by infectious endocarditis, produces seeding of the systemic circulation and may result in a brain abscess.[131] The presence of headache or other neurologic symptoms in any preoperative patient with tetralogy of Fallot, even in the absence of fever, warrants investigation into the possibility of this serious and potentially fatal complication.

Paroxysmal Hypoxemic Spells

The underlying mechanisms that result in "tetralogy spells" are described in this chapter in the Physiology and Hemodynamics section. Regardless of the underlying mechanism responsible for these spells, the clinical manifestations are similar and are characterized by increasing cyanosis and an increased rate and depth

of respiration. Hypoxemic spells can occur in any patient with an intraventricular communication and a right-to-left shunt at ventricular level and thus may be found in patients who are acyanotic at rest as well as in patients with tetralogy of Fallot and pulmonary atresia. As a result of the increased right-to-left shunt at ventricular level, whatever the underlying mechanism, forward flow across the right ventricular outflow tract is reduced.

Hypoxemic spells are usually self-limited and of less than 15 to 30 minutes duration. In addition to trying to comfort the patient during one of these episodes, it is also advisable to have the child assume a knee–chest position. In an older child, this can be accomplished by squatting, or by raising the knees to the chest in the supine or prone position. Similarly, the infant or small child can be held over the parent's shoulder with the knees drawn up against the infant's chest. It is likely that squatting, or assuming a knee–chest position, causes increased peripheral resistance in the lower extremities and this, in turn, promotes an increase in pulmonary blood flow.

In a hospital situation, oxygen is administered by face mask during a hypoxemic spell; if the oxygen does not appear beneficial, it should be removed since it may irritate the child. If the patient's hypoxemic episode does not appear to be resolving, morphine sulfate can be administered either intramuscularly, subcutaneously, or intravenously in a dose of 0.1 mg/kg of body weight. The effectiveness of morphine sulfate in treating a hypoxemic spell has been known for many years, but its exact mechanism of action is still unclear. It may have a direct relaxing effect on the subpulmonary infundibulum or its action may be mediated through an effect on the central nervous system, or by a peripheral vagotonic effect. Since morphine can be administered intramuscularly, it is valuable to use this drug for initial management of a hypoxemic spell when an intravenous route is unavailable. Once an intravenous line has been placed, the dose of morphine sulfate again can be repeated or additional pharmacologic agents can be administered directly into the venous system. It is important to remember that metabolic acidosis appears rapidly after the onset of a hypoxemic spell and thus sodium bicarbonate in a dose of 1 mEq/kg can be given empirically as soon as intravenous access is available. If these measures are unsuccessful, a beta-blocking agent such as propranolol is extremely valuable in the management of a hypoxemic spell.[132] Propranolol is given intravenously to a maximum total dose of 0.1 mg/kg of body weight. It must be remembered that 1 mg intravenously is the standard adult dose of propranolol. Thus, the total calculated dose should be diluted with 10 mL of fluid in a syringe and no more than half of the calculated dose should be given initially as an intravenous bolus. The remainder can be given slowly over the next 5 to 10 minutes if it appears that the initial intravenous dose has not been effective in starting to reverse the hypoxemic spell. Any time intravenous propranolol is used, isoproterenol should also be available to reverse the effects of overdosage of the beta-blocking agent.

In the same way that the knee–chest position improves pulmonary blood flow by increasing systemic resistance, intravenous infusion of fluid for volume expansion, or the administration of a peripheral vasoconstrictor such as phenylephrine, will have a similar effect. In the unusual circumstance where all of these physical and pharmacologic maneuvers have been unsuccessful, general anesthesia can be utilized to abort a hypoxemic spell. In this situation, an emergency systemic pulmonary artery anastomosis should also be considered. Fortunately, this has been rarely necessary in our experience.

Propranolol has also been used in the long-term nonoperative management of paroxysmal hypoxemic spells.[133,134] It is administered orally in a dose of 1 to 4 mg/kg of body weight per day in three or four divided doses. Its major usefulness would be in the management of hypoxemic spells in patients who were not candidates to have surgical management. For example, in a patient who has normal or increased pulmonary blood flow and is too small for complete repair, a systemic to pulmonary artery anastomosis might result in excessive pulmonary blood flow. In such a patient, the use of propranolol might enable an attempt at complete repair to be deferred until the patient was older and the risk of operation lower.

SURGICAL MANAGEMENT OF TETRALOGY OF FALLOT

Definitive surgical repair is the ultimate goal of the management of tetralogy of Fallot and tetralogy of Fallot with pulmonary atresia. In the asymptomatic patient, the timing of surgical management remains controversial with some centers advocating a complete repair in infancy while others prefer to perform repair during early childhood. Most would agree that some form of surgical management is indicated for the symptomatic patient with severe cyanosis, polycythemia or hypercyanotic "spells." A definitive, single-stage operation is preferred at any age but may not be possible for any of a number of reasons that include the size of the patient, small caliber of the pulmonary arteries, or coronary artery anomalies. Surgical expertise in the individual center must also be considered. These factors will be discussed in more detail in the section on Complete Repair. When surgical intervention becomes necessary in the symptomatic patient who is not a good candidate for complete repair, a palliative procedure is performed to increase pulmonary blood flow until definitive surgical correction is possible.

Systemic to Pulmonary Artery Anastomoses

Subclavian to Pulmonary Artery Anastomoses

In 1945, Blalock and Taussig[2] described the surgical creation of an artificial ductus arteriosus using an end-to-side anastomosis between the subclavian artery and the pulmonary artery (Fig. 63–17). This procedure marked the beginning of the era of surgical management of complex cyanotic congenital heart disease. The technique that is currently employed to perform this "classic" Blalock-Taussig (B-T) shunt is similar to that originally described by Blalock and Taussig with only a few modifications. The procedure is performed through a lateral thoracotomy on the side opposite the aortic arch. This is preferred because the subclavian artery originating from the brachiocephalic artery has more mobility. In addition, the angle from the brachiocephalic artery is less acute and thus kinking is less likely as compared to using the subclavian artery that arises directly from the aorta on the same side as the aortic arch. The subclavian artery is divided at the origin of its branches and the vertebral artery is ligated. This latter step is essential to avoid the problem of "subclavian steal" (see below) postoperatively. The proximal stump of the subclavian artery is then anastomosed to the side of the right pulmonary artery just proximal to the first branch.

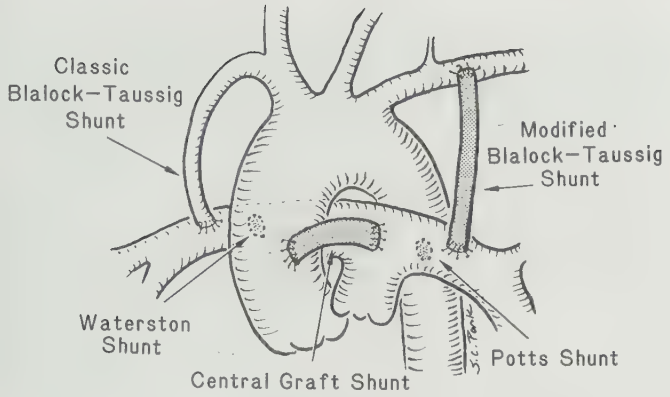

Fig. 63–17. Diagram illustrating the various systemic to pulmonary artery anastomoses.

The classic Blalock-Taussig shunt can be performed in infants and children and provides excellent long-term palliation.[135,136] With this procedure, as compared to other forms of systemic to pulmonary artery anastomoses, the size of the patient's subclavian artery, rather than the size of the surgical anastomosis will limit the volume of pulmonary blood flow. Thus, the incidence of complications from excessive pulmonary blood flow such as congestive heart failure and pulmonary hypertension are extremely low following the Blalock-Taussig anastomosis.[98,99]

In infants younger than 6 months of age, especially in the newborn, the subclavian artery is of relatively small size and short length. Although the classic B-T shunt can be performed successfully, especially with the currently available microsurgical techniques, this shunt may be prone to thrombosis or problems with inadequate blood flow. As a result, a modified form of Blalock-Taussig anastomosis has become popular over the last decade for use in patients under 6 months of age, especially small infants.[137–140] This procedure is usually performed on the same side as the aortic arch as compared to the opposite side in the classic B-T shunt (Fig. 63–17). This modified B-T shunt consists of an interposition graft of synthetic material, usually expanded polytetrafluorethyelene (PTFE or Gore-Tex) between the subclavian artery and the pulmonary artery. A prosthesis of greater diameter than that of the subclavian artery, usually 5 to 6 mm, is sutured to the side of the undivided subclavian artery, with the other end of the graft sutured to the side of the pulmonary artery. This modified B-T shunt has the advantage of the classic type of shunt in that the subclavian artery is still the limiting factor in pulmonary blood flow. On the other hand, it is easier to perform in small infants, does not require sacrificing the subclavian artery and allows for a larger surgical anastomosis thus providing for a potential increase in the magnitude of pulmonary blood flow as the patient grows and the subclavian artery increases in size.

In addition to the low incidence of problems from excessive pulmonary blood flow, both forms of Blalock-Taussig shunt also have additional advantages compared to the other types of systemic to pulmonary artery anastomoses (see below). These include the fact that the pericardium is not entered thus avoiding problems with pericardial adhesions at the time of future procedures. In addition, these B-T shunts are easiest to close at the time of complete repair simply by ligation of the distal portion of the shunt just proximal to the anastomosis with the pulmonary artery. Although some distortion of the pulmonary artery usually occurs with all forms of systemic to pulmonary artery anastomoses, this is usually limited to "tenting" of the pulmonary artery in patients who have had a B-T shunt as compared to the more serious distortion and kinking of the pulmonary arteries that occurs with other procedures.

In addition to problems of excessive pulmonary blood flow and distortion of the pulmonary arteries, a number of less serious complications occur following B-T anastomosis. Since the phrenic nerve, the recurrent laryngeal nerve and the cervical sympathetic chain are found in the area of the dissection, complications related to dysfunction of these nerves may follow such operations. These include diaphragmatic paralysis (phrenic nerve), vocal cord paralysis (recurrent layrngeal nerve), and Horner's syndrome (ptosis, miosis, and anhydrosis—cervical sympathetic chain).[51,136,139] Chylothorax or hemothorax are relatively short-term problems that can occur following all shunt procedures. Problems specifically related to use of the subclavian artery are uncommon but include subclavian vascular insufficiency as a result of poor collateral blood flow (even less common with the modified form of shunt that does not sacrifice the subclavian artery) and subclavian steal syndrome. This latter problem is a form of basilar artery insufficiency as a result of "vertebral steal" from the cerebral circulation to provide collateral flow into the distal subclavian artery.[141] This problem should no longer occur following a B-T shunt since the vertebral artery is almost always ligated at the time of operation.

Aorta to Pulmonary Artery Anastomoses

A number of other procedures have been described that involve either direct connection or graft interposition between the aorta and the pulmonary artery (Fig. 63–17). The Potts operation[3] was first described in 1946 shortly following the Blalock-Taussig operation, and consists of a direct anastomosis between the descending aorta and the left pulmonary artery. An intrapericardial, direct anastomosis between the ascending aorta and the right pulmonary artery was described by Waterston in 1962[142] and Cooley and Hallman in 1966.[143] The central aortopulmonary shunt followed the introduction of polytetrafluorethylene (PTFE or Gore-Tex) and is similar to the Waterston shunt but instead is a graft interposition between the ascending aorta and the right or main pulmonary artery.[144,145]

For approximately two decades following its introduction, the Potts anastomosis was quite popular and was the procedure of choice in many centers for infants under one year of age. This procedure was recommended because of the small size of the subclavian artery and concern about poor success with the B-T shunt in this age group.[146] Although the Potts operation provided excellent palliation, it was difficult to take down this anastomosis at the time of complete repair. It thus became much less frequently performed after the mid 1960s when the ascending aorta to right pulmonary artery shunt became popular. This latter procedure, the Waterston anastomosis, also was easy to perform in the small infant but was more easily closed from the median sternotomy approach at the time of corrective surgery. Since the late 1970s, the central shunt using a graft interposition has been used for similar reasons. In contrast to the Blalock-Taussig anastomosis where the pulmonary blood flow is limited by the size of the patient's subclavian artery, the size of the aortopulmonary communication with these other anastomoses is controlled by the tech-

nique of the surgeon. On occasion, the anastomosis would be too small and the procedure would not adequately relieve the patient's cyanosis. More commonly, excessive pulmonary blood flow from a large anastomosis resulted in congestive heart failure in 20% or more of survivors following the Potts or Waterston anastomosis.[135,146–148] Pulmonary hypertension, as a result of this excessive pulmonary blood flow, led to the development of pulmonary vascular disease in many of these patients.[146–148] An unusual problem has also been encountered following the Potts anastomosis. Some patients have late development of pulmonary hypertension or congestive heart failure as a result of progressive enlargement of the anastomotic channel some years later.[146]

Distortion of the pulmonary artery occurs at the site of anastomosis following most shunt procedures but is not usually an important problem with the classic Blalock-Taussig, modified Blalock-Taussig or central shunts. On the other hand, significant acquired pulmonary artery stenosis has been found following the Potts and particularly following the Waterston anastomoses.[135,147,148] The central Gore-Tex shunt does not seem to have as much a problem with either excessive pulmonary blood flow or distortion of the pulmonary artery as compared to the Waterston or Potts anastomosis. Early results with this procedure from many centers were disappointing, but subsequent modifications of the surgical technique have demonstrated excellent palliation, especially in the very small infant in whom it may be more difficult to perform a modified Blalock-Taussig shunt.[145]

Complete Repair

Definitive surgical repair of tetralogy of Fallot consists of closure of the ventricular septal defect and relief of the right ventricular outflow tract obstruction. The first successful open intracardiac repair of tetralogy of Fallot was performed by Lillehei in 1954 by means of "controlled cross-circulation" using another human as the "oxygenator."[4] The pump oxygenator was first used by Kirklin et al. at the Mayo Clinic in 1955.[20] In the more than three decades since then, major changes have occurred with the addition of techniques such as patch enlargement of the right ventricular outflow tract, transannular outflow patches and the use of conduits or homografts in the management of severe diffuse outflow obstruction or pulmonary atresia. Together with advances in surgical technique, cardiopulmonary bypass and intraoperative management, major advances in anesthesia and postoperative care have resulted in the expectation that over 90% of patients who undergo complete repair of tetralogy of Fallot will survive to adulthood with a good long-term functional result.[148]

Primary Repair versus Palliation

It is generally agreed that definitive repair should be performed as a primary procedure at any age if the operation can be performed at a low risk and with a reasonable expectation of good result. However, the criteria for patient selection and timing of complete repair are still controversial. Some groups have advocated primary repair of tetralogy of Fallot in symptomatic infants with favorable anatomy under a year of age, regardless of size.[150–152] Contraindications would include an anterior descending coronary artery arising from the right coronary artery, severely hypoplastic pulmonary arteries, or pulmonary atresia. Kirklin et al.[153,154] have studied the incremental risk factors involved in performing primary repair at a young age. They concluded that primary repair without a transannular patch was as safe as a two-stage approach (shunt then repair) when an infant was over 6 months of age (0.35 m^2). When a transannular patch was necessary for primary repair, the two-stage approach was felt to be safer when an infant was under 9 months of age or had a body surface area of less than 0.48 m^2. In addition to small size of the pulmonary arteries and/or the pulmonary valve annulus, other factors associated with an increased risk of early repair include: Other abnormalities of the pulmonary arteries such as anomalous origin of one artery, peripheral pulmonary arterial stenoses, or the presence of major associated anomalies. Despite all of these studies and many others that have not been quoted, the ideal criteria for primary repair versus a two-stage operation have not yet been determined, and must be individualized by center. The size of the pulmonary arteries seem to be the major limiting factor and the question "How small is too small?" remains unanswered.

Operative Procedures

Complete intracardiac repair consists of patch closure of the ventricular septal defect and relief of the right ventricular outflow tract obstruction. In patients over 1 year of age, most surgeons use conventional cardiopulmonary bypass with mild to moderate hypothermia (25 to 30°C). Cold cardioplegia together with topical cooling may also be used.[20] These latter techniques provide myocardial protection and increase the allowable time of anoxic arrest due to aortic cross clamping. Profound hypothermia with circulatory arrest is generally used in infants under 1 year of age[151,152] and some centers use profound hypothermia with low flow cardiopulmonary bypass in all but small infants under 4 months of age.[153] In most cases, especially when there are multiple levels of pulmonary stenosis, a vertical incision in the right ventricle is used for repair. This vertical incision provides excellent exposure and is useful if a transannular outflow patch is found to be necessary.[20] A transverse right ventriculotomy is preferred by some surgeons especially when the use of a transannular outflow patch is not planned. This latter type of incision is mandatory in the situation where an anomalous coronary artery crosses over the right ventricular outflow tract and might be injured by a vertical incision. The right atrium is usually opened during the operation to close an atrial septal defect or to suture a patent foramen ovale. Transatrial closure of ventricular septal defects is now commonplace and some centers have reported complete repair of tetralogy of Fallot using this approach.[20,155,156] If the patient has had a prior systemic to pulmonary artery anastomosis, the necessary dissection in the preparation for closure of the shunt is performed prior to the institution of cardiopulmonary bypass. Once this has been accomplished and bypass has been established, this shunt is then closed. This is done by direct vision, and an accompanying pulmonary arterioplasty may be necessary in patients who have undergone a Waterston or Potts anastomosis while ligation of the distal anastomosis is usually sufficient in patients who have classic or modified B-T shunt or a central shunt.

The approach to closure of the ventricular septal defect and management of right ventricular outflow obstruction is similar regardless of whether a transatrial or ventriculotomy approach is used. After the initial incision is made and the internal anatomy of the right ventricle is inspected, resection of infundibular and other hypertrophied muscle bands is carried out to enhance visualization of the ventricular septal defect and facilitate its repair.

The ventricular septal defect is closed using a patch of synthetic material, either Dacron or Teflon. The patch is sutured on the right ventricular side of the ventricular septal defect with particular care taken to avoid injury to the aortic valve leaflets or to the conduction system. In a patient with a membranous ventricular septal defect, the bundle of His runs along the posteroinferior margin of the defect and the crest of the interventricular septum. Sutures are placed superficially and as far to the right ventricular side of the defect as possible to avoid damage to this structure.

Adequate relief of right ventricular outflow obstruction is essential for successful repair of tetralogy of Fallot. Isolated infundibular or valvar stenosis may be present, but more commonly additional areas of stenosis are present at the level of the pulmonary valve annulus, or in the pulmonary arteries. Pulmonary arterial stenosis may be supravalvar, peripheral, or the pulmonary arteries may be diffusely hypoplastic. It is not unusual for multiple levels of stenosis to be present in the same patient. On some occasions, infundibular resection alone is sufficient to relieve the subpulmonary stenosis, but placement of a patch to further widen the right ventricular outflow tract is generally necessary. In the past, autologous pericardium has been used for this outflow patch but this material has a tendency to aneurysmally dilate on long-term followup, especially if there is residual stenosis. Many centers have thus begun to use a patch of synthetic material, either Dacron or Gore-Tex, or bovine pericardium, instead of autologous pericardium. The pulmonary valve is also inspected and valvar stenosis is relieved as much as possible. If further sites of downstream obstruction are present and these preceding measures are not sufficient enough to lower the right ventricular pressure, it may be necessary to extend the outflow tract patch across the pulmonary valve annulus, onto the pulmonary artery (Fig. 63–18). When pulmonary artery hypoplasia is present the patch is extended onto the pulmonary artery branches.

In infants where transannular patching increases the risk of operation to such a degree that a two-stage operation may be safer,[153] or in other patients where diffuse hypoplasia of the pulmonary arteries may preclude a successful repair at any age, prediction of the postoperative right ventricular pressure would have considerable value. Kirklin et al.[153] have suggested that a postoperative right to left ventricular pressure ratio ($P_{RV/LV}$) of less than 0.75 will be associated with a good functional result if the ventricular septal defect is adequately closed and the pulmonary valve ring is intact. To determine whether a transannular outflow patch would be required to relieve a postoperative $P_{RV/LV}$ of greater than 0.75, intraoperative measurement of the pulmonary annulus by means of Hegar dilators has been used. A pulmonary valve annulus that is less than 50% of the diameter of the ascending aorta,[156] or less than a minimum acceptable diameter from a table of normal values,[157] has been used as an indication for the necessity of a transannular outflow patch to achieve a successful surgical result with low mortality. Other centers have used different decision approaches.

On the other hand, in the infant who requires surgical intervention, or at any age when significant pulmonary artery hypoplasia is present, preoperative prediction of a postoperative $P_{RV/LV}$ greater than 1.0 would be of considerable value. In these patients, a palliative procedure would be indicated instead of an attempt at complete repair that might well be unsuccessful. A number of methods have been developed to predict the ratio of right-to-left ventricular pressure after repair on the basis of preoperative cineangiographic measurement. Blackstone et al.[91] have developed a formula to predict postrepair $P_{RV/LV}$ related to the diameter of the right and left pulmonary arteries and the pulmonary valve annulus as measured from preoperative cineangiograms and normalized to the patient's descending thoracic aorta. Another approach was taken by Nakata et al.[89] who calculated the pulmonary artery area index by measurement of right and left pulmonary arteries from preoperative cineangiograms. Although their index was not used to predict postoperative right ventricular pressure, those patients with a pulmonary artery area index of less than 60% of normal

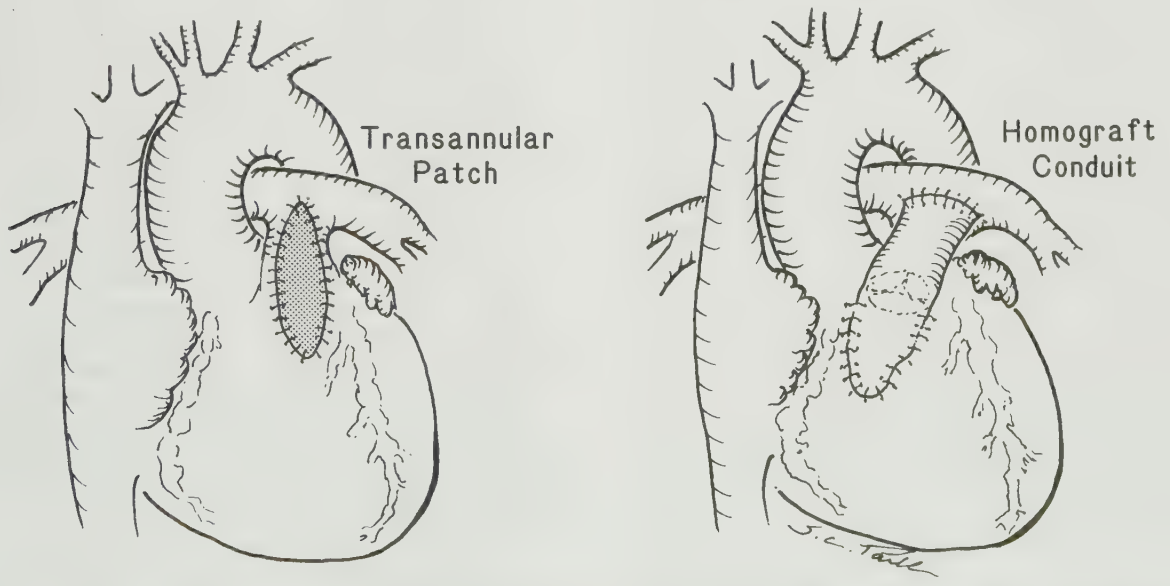

Fig. 63–18. Diagram illustrating surgical management of severe right ventricular outflow obstruction. Left: Transannular outflow patch; Right: Use of an aortic homograft conduit.

either had severe problems with low cardiac output and congestive heart failure or died in the postoperative period. Naito et al.[90] used still another method, the calculation of left ventricular end diastolic volume index, and suggested that those patients with an index of less than 30 mL/m^2 were not adequate candidates for complete repair and should undergo palliation if a surgical procedure was necessary.

Although all of these methods for estimating the success of complete repair have considerable influence on the type of procedure performed in infants and small children, complete repair is usually attempted in older children. In general, the relief of right ventricular outflow tract obstruction with a transannular outflow patch is well tolerated despite the presence of postoperative pulmonary regurgitation.[93,149] However, some patients will poorly tolerate the postoperative pulmonary regurgitation especially if there is increased pulmonary vascular resistance from a previous systemic to pulmonary artery shunt, or distal pulmonary artery stenosis. In these patients, a valved external conduit, either a Dacron conduit with a porcine heterograft valve or a homograft, has been used successfully.[158,159] Other indications for use of an external conduit include repair in a patient with an anomalous anterior descending coronary artery that arises from the right coronary artery, crosses the right ventricular outflow tract, and thus interferes with adequate relief of the outflow obstruction by standard techniques[31,34]; or in patients with tetralogy of Fallot and pulmonary atresia.

Pulmonary Artery Hypoplasia or Pulmonary Atresia

In some patients with severe pulmonary artery hypoplasia or with pulmonary atresia, continuity between the right ventricle and the pulmonary arteries can be achieved at definitive repair using a transannular outflow patch.[160,161] For this to be possible there must be a pulmonary artery trunk with confluent central pulmonary arteries. In these cases, surgical correction does not differ from that of other patients with tetralogy of Fallot requiring a transannular patch. More commonly, a conduit connecting the pulmonary arteries to the right ventricle is required for adequate relief of the obstruction[160,161] (see Fig. 63–18). Reconstruction of the right ventricular outflow tract using a valveless conduit was first reported by Rastelli in 1965.[162] The most commonly used conduits in current clinical practice are valved. They are either made of Dacron with porcine or bovine valves, or aortic or pulmonary homografts.

A number of complications have been related to the use of Dacron conduits. One of the reasons for failure of these conduits is improper positioning below the sternum. Ideally they should be toward the left of the sternum in order to avoid stenosis produced by sternal compression.[163] The development of gradients within the conduits appears to be a function of time. Conduit failure as high as 30% in 6 years has been reported.[164] Stenoses may occur at the site of conduit anastomosis with the right ventricle, with the pulmonary arteries and even within the conduit itself.[165] Intraconduit obstruction is usually related to calcification of the heterograft valve or to a consequence of a hypertrophic neointima that develops inside the conduit. This neointima can become obstructive per se, but it is also susceptible to dissection with resultant obstruction of the conduit. This can occur spontaneously or at the time of cardiac catheterization. Conduit valve insufficiency is very common.

The use of cryopreserved, antibiotic sterilized aortic and pulmonary homografts has become increasingly popular. Even though calcification of the homografts leading to homograft stenosis is a well-recognized problem, the incidence of reoperation following the use of these conduits appears to be lower.[166,167] Homograft valve stenosis and insufficiency also appear to be less of a problem. The use of a pulmonary homograft is particularly attractive in patients with severe stenosis at the bifurcation of the main pulmonary artery or when the right and left pulmonary arteries are discontinuous.

Care must be taken at the time of establishing continuity between the right ventricle and the pulmonary arteries if there is severe proximal pulmonary artery hypoplasia. These patients usually have dual pulmonary blood supply from true pulmonary arteries and major aortopulmonary collateral arteries. At least half of the segments of both lungs must be supplied by true pulmonary arteries. In these patients the predicted postoperative $P_{RV/LV}$ may be very high. Intraoperative $P_{RV/LV}$ of > 0.7 is associated with a high surgical mortality. When found, it is advisable to create a hole in the patch closing the ventricular septal defect to act as a "runoff" for the right ventricular hypertension.[168]

The presence of major aortopulmonary collateral arteries requires special management considerations. Before any surgical procedure involving the use of the aortopulmonary collaterals can be undertaken, exact definition of the segments of lung supplied by true pulmonary arteries and those supplied by collateral vessels is mandatory. This is achieved at the time of the cardiac catheterization with selective injections in the pulmonary arteries and the different collateral arteries. Most aortopulmonary collateral arteries have an area of stenosis, reducing the pressure in these vessels and protecting the pulmonary vascular bed that it supplies from developing pulmonary vascular disease. Some segments of lung may be supplied by unobstructed collateral arteries and face systemic pressures. These segments are at risk of developing pulmonary vascular disease.

As much of the pulmonary vascular bed as possible should receive its blood flow from the right ventricle. This gives rise to the concept of "unifocalization" of the pulmonary blood supply. This requires connecting the major aortopulmonary collateral vessels to the true pulmonary arteries at the level of the hilum. This type of surgery is technically difficult since many of the collateral vessels follow an intraparenchymal course.[169] If a lung segment has a dual supply, and thus receives blood flow from the true pulmonary arteries as well as from collateral arteries, then the collateral vessel can be safely ligated. Some collateral arteries may not be accessible to establishing continuity with the central pulmonary arteries and need to remain intact at the time of complete repair. These patients may have excessive pulmonary blood flow and develop congestive cardiac failure. Surgical ligation or embolization of these vessels at the time of postoperative cardiac catheterization would be indicated. The adequacy of alternative blood supply to the lung segment that is being embolized must be established prior to any of these procedures since pulmonary infarction has been described after ligation of a collateral that was the sole supply to a lung segment.[160,161] Successful embolization has been reported using tissue adhesive,[170] Gianturco coils,[171] and detachable balloons.[172]

LATE RESULTS

This section will mainly consider the long-term results following complete repair of tetralogy of Fallot or tetralogy of Fallot with

pulmonary atresia. Firstly, a brief discussion of the outlook for patients who have not undergone complete repair is warranted. Although survival to adulthood without benefit of surgical palliation or repair has been reported, less than 5% of untreated patients will survive beyond 25 years of age.[173,174] A small group of patients who underwent systemic to pulmonary artery anastomoses during the first decade that these procedures were available did not undergo complete repair when it later became possible. This was generally because these patients had achieved an excellent functional result from their palliative procedure and did not wish to undergo another operation. The majority of these patients eventually required complete repair, usually as a result of increasing symptoms due to progressive hypoxia or right and left ventricular dysfunction. This group certainly demonstrated that survival into adulthood was possible solely with palliative surgery but that complete repair ultimately became necessary.[175]

There are two other groups of patients for whom complete repair may not be possible. One group consists of patients with severe pulmonary artery hypoplasia and either pulmonary stenosis or pulmonary atresia. In these patients, if a systemic to pulmonary artery anastomosis or an outflow tract reconstruction procedure is not successful in alleviating hypoxia or polycythemia, then it is unlikely that these patients will survive into the second or third decade of life. In general, if palliative procedures achieve an adequate result, then the pulmonary arteries are usually of sufficient size to attempt complete repair. The second group consists of those patients who have developed pulmonary vascular disease due to a large systemic to pulmonary artery anastomosis. This was common with the Potts anastomosis and in more recent years following a Waterston shunt.[146–148] Included in this group are patients with tetralogy of Fallot and pulmonary atresia with pulmonary blood flow occurring through large, unrestrictive systemic to pulmonary collateral arteries. These latter two groups have increased pulmonary blood flow as a result of their surgically created or naturally occurring systemic to pulmonary artery connection. This leads to problems related to increased pulmonary blood flow and congestive heart failure rather than decreased pulmonary blood flow and hypoxia. The end result of this large unrestricted pulmonary blood flow is usually the development of pulmonary vascular disease which precludes complete repair. These patients would be expected to survive into the third or fourth decade of life and would ultimately develop problems with hypoxia, polycythemia, and ventricular dysfunction in a manner similar to patients who develop pulmonary vascular disease from other types of congenital heart disease.

In most centers, over 90% of patients who undergo complete repair of tetralogy of Fallot will survive to adulthood and have a good functional long-term result.[149] Since the long-term survival of patients having undergone successful repair of tetralogy of Fallot is very close to the expected survival of an age, race, and sex-matched population,[176] this suggests that most mortality from complete repair of tetralogy of Fallot occurs perioperatively or within the first few years following operation. Although postoperative hemodynamic abnormalities such as residual ventricular septal defects or some degree of right ventricular outflow tract obstruction are often present, these are usually not severe enough to require reoperation and have not yet been demonstrated to affect long-term mortality. Other problems such as pulmonary regurgitation and arrhythmias may also influence the long-term results and survival.

Residual Pulmonary Stenosis

Postoperative right ventricular hypertension is usually due to residual pulmonary stenosis, a residual ventricular septal defect, or both. Pulmonary hypertension secondary to pulmonary vascular disease is uncommon but may be found in patients with a previous systemic to pulmonary artery shunt, particularly the Potts anastomosis. Residual pulmonary stenosis may occur at the level of the pulmonary valve or the annulus and is due to either inadequate relief of obstruction at the time of operation or recurrent valvar stenosis. Residual obstruction may be apparent in the early postoperative period and Kirklin et al. have recommended reoperation for placement of a transannular outflow patch, even as early as 24 hours postoperatively, if right ventricular hypertension of greater than 70 to 80% of systemic level persists.[20] Pulmonary artery stenosis either at the pulmonary artery bifurcation or more distally, is the most common cause of residual right ventricular hypertension. This may occur at the site of distal insertion of a pulmonary artery patch, or at the site of pulmonary artery reconstruction following a systemic to pulmonary artery anastomosis (in particular the Waterston anastomosis). The combination of distal pulmonary artery stenosis and pulmonary regurgitation postoperatively produces both right ventricular volume and pressure overload and may result in considerable right ventricular dysfunction. Thus, if significant pulmonary artery stenosis is anticipated at the time of initial repair or following reoperation, insertion of a valve in the pulmonary position, or the use of a valved conduit, has been recommended.[20]

Some degree of residual pulmonary stenosis is present in most patients who have undergone repair of tetralogy of Fallot.[93,96,149] In about two-thirds of cases this is usually either trivial or mild enough so that right ventricular pressure is less than 50% of systemic level. In approximately another 25% of patients a moderate degree of right ventricular hypertension is present with right ventricular pressure over 50% but less than about 75% of systemic level. In these patients reoperation is usually not required unless a significant residual ventricular septal defect is also present. Residual right ventricular hypertension greater than 75% of systemic level and requiring reoperation occurs in as many as 10% of patients.[177]

Pulmonary Regurgitation

There has been considerable debate over the years about the longterm effect of the pulmonary regurgitation that is produced by pulmonary valvectomy and/or the use of a transannular outflow patch. Unless this occurs in conjunction with significant residual pulmonary stenosis, even wide open pulmonary regurgitation is usually well tolerated and most patients are entirely free of symptoms.[93,96,149] On the other hand patients with pulmonary regurgitation have larger cardiothoracic ratios on chest roentgenogram and larger right ventricular volumes.[178] In addition, incompetence of the pulmonary valve was associated with either reduced exercise capacity or other abnormalities demonstrated at postoperative stress exercise testing.[96] Thus, although almost all of these patients appear to be functionally normal, these abnormalities of right ventricular size and function may be a source of problems over the long term. The question of whether continued pulmonary re-

gurgitation will have a deleterious effect on right ventricular function and ultimately affect long-term survival remains to be answered.

Residual Ventricular Septal Defect

The frequency of small or large residual ventricular septal defect varies, but may be as high as 20% of patients who have undergone repair of tetralogy of Fallot.[93,96,149] This communication may result from dehiscence in a small area of the patch or possibly just excessive space between two sutures. A major dehiscence will result in a large left-to-right shunt and will usually require reoperation. A second or multiple ventricular septal defects also may be present in the trabecular muscular septum in patients with tetralogy of Fallot. Even if this defect is identified preoperatively, it may be covered by trabecular muscle on the right ventricular side of the septum and may be extremely difficult to localize and repair at the time of operation. It is extremely important not only to identify the presence of this additional type of defect, but also to determine its size preoperatively. If this defect is assessed to be small, it will not contribute a large left-to-right shunt in the postoperative period, and the recommendation is made to the surgeon that closure of the defect is not necessary at the time of operation. On the other hand if a large left-to-right shunt is expected because of the size of the defect then an attempt at closure should be made at the time of operation even if it means approaching the defect through the apex of the left ventricle. This latter approach is used only if an extremely large defect is present since the addition of a left ventriculotomy at the time of repair is likely to result in poor cardiac output and bilateral ventricular dysfunction in the postoperative period.

In most patients a residual ventricular septal defect with a pulmonary to systemic flow ratio (Q_p/Q_s) of less than 1.5/1 is well tolerated and reoperation is usually not recommended. If the Q_o/Q_s is greater than 1.5/1 to 2/1, then reoperation is recommended.[149,177] This magnitude of residual shunt will ultimately produce ventricular dysfunction especially if it is present in combination with other problems such as right ventricular hypertension due to residual pulmonary stenosis. Reoperation for a residual ventricular septal defect is usually successful with little additional mortality. It results in improvement in ventricular function and a predicted beneficial effect on long-term survival.

Ventricular Function

Abnormalities of right or left ventricular function may occur as a result of a residual left-to-right shunt, residual pulmonary stenosis, or pulmonary insufficiency.[95,96] These may occur alone or in combination. A residual left-to-right shunt with resultant left ventricular dysfunction and congestive heart failure may occur from a residual ventricular septal defect or a systemic to pulmonary artery anastomosis that was not effectively closed at repair.[179] In addition, large systemic to pulmonary collateral arteries may also produce a similar problem. When large collateral arteries are identified preoperatively some attempt should be made to ligate these vessels at the time of operation. Unfortunately this is often unsuccessful and a number of techniques for occlusion of these vessels in the cardiac catheterization laboratory have been used to avoid reoperation.[170–172] If one of these procedures is not successful in alleviating a large left-to-right shunt, then reoperation through a posterolateral thoracotomy may be necessary to ligate these vessels at their origin from the descending aorta.

Right ventricular dysfunction is usually a result of the combination of volume overload from a residual ventricular septal defect and/or pulmonary regurgitation and pressure overload from residual pulmonary stenosis. The combination of pulmonary regurgitation with or without pulmonary artery stenosis has been discussed in the preceding paragraphs. Even in patients with a good hemodynamic result, right ventricular dysfunction is evident in the early postoperative period with right ventricular end diastolic and mean right atrial pressures usually in the range of 12 to 15 mm Hg or higher.[180] It has been recognized for many years now that a right atrial pressure in the normal range of 5 to 6 mm Hg or less in the first 24 hours following tetralogy of Fallot repair is a sign of hypovolemia and indicates the need for immediate volume expansion. These "normal" elevated right ventricular end diastolic and right atrial pressures are presumed to reflect temporary right ventricular dysfunction. Although these elevated pressures may persist for a few weeks and are often found at cardiac catheterization within 1 month postoperatively, this appears to be a temporary phenomenon since most patients with good ventricular function exhibit normal right ventricular end diastolic and right atrial pressures at catheterization 1 to 2 years postoperatively.[94]

Left ventricular function is also compromised in the early postoperative period and many patients require temporary inotropic support in the first 24 hours.[180] It is common for patients who have had repair of tetralogy of Fallot to receive digoxin therapy postoperatively but this can usually be discontinued within a few months unless the patient has congestive heart failure from residual abnormalities. Left ventricular dysfunction may also be found postoperatively in patients with coronary artery abnormalities. An anomalous or accessory anterior descending coronary artery arising from the right coronary artery and crossing the right ventricular outflow tract is at risk for injury during repair.[31,34] If this arterial anomaly is not recognized preoperatively, a vertical incision in the right ventricular outflow tract will transect that coronary artery especially if it is necessary to extend the incision across the pulmonary valve annulus. A myocardial infarction will then occur in the areas supplied by this coronary artery with resultant postoperative left ventricular dysfunction that persists over the long term. Since little can be done to reverse the damage that occurs due to injury to the coronary artery, it is clearly essential that this problem be recognized preoperatively. When it is present, the repair is performed through a horizontal ventriculotomy or through a transatrial approach and a right ventricle to pulmonary artery conduit is used if the right ventricular outflow obstruction cannot be relieved adequately by infundibular resection and/or pulmonary valvotomy alone.

Arrhythmias and Conduction Abnormalities

Atrioventricular conduction abnormalities are common following repair of tetralogy of Fallot and are infrequent preoperatively (see section on Cardiac Catheterization in this chapter).[107,108] Right bundle branch block results from injury to the right bundle branch but in itself appears to be benign. The appearance of postoperative bifascicular block (left axis deviation with right bundle branch block), especially in a patient who had transient complete AV block at the time of surgery, has been considered a possible warning sign for development of late complete AV block.[72,73] However,

followup in the majority of these patients has been benign. Permanent complete atrioventricular block following repair of tetralogy of Fallot usually necessitates the insertion of a permanent pacemaker. Even if the ventricular rate is rapid, insertion of a pacemaker would definitely be indicated if the atrioventricular block occurs below the level of the bundle of His.[74] Thus, in a postoperative patient, an attempt should be made to determine the site of atrioventricular block by recording His bundle electrograms if it is contemplated *not* to insert a permanent pacemaker.

Fortunately, complete atrioventricular block is now uncommon following repair of tetralogy of Fallot. However, if complete atrioventricular block occurs, especially with a slow idioventricular rhythm, many surgeons would consider insertion of permanent pacing wires at the time of repair. External pacing through temporary ventricular epicardial pacing wires will be sufficient to maintain heart rate during the early postoperative period. If the atrioventricular block does not resolve within 2 weeks, then the permanent pacing wires will already be in place thus enabling a simpler operation for insertion of the permanent pacemaker.

Premature ventricular contractions (PVCs) may be found at rest or may be induced by exercise in patients who have undergone repair of tetralogy of Fallot. In many cases these are benign and have little significance. On the other hand serious ventricular arrhythmias may occur and these include multiform PVCs, ventricular tachycardia, or ventricular fibrillation. Although it was previously felt that sudden death in patients who have undergone repair of tetralogy of Fallot was a manifestation of the late onset of complete heart block,[75] it is currently believed that sudden death is more likely due to serious ventricular arrhythmias.[76,77] A number of investigators have suggested that these arrhythmias are more common in patients with significant residual hemodynamic abnormalities. In most centers stress exercise testing and 24-hour ambulatory monitoring are routinely performed in patients who have undergone repair of tetralogy of Fallot. This is especially true in those patients who are found to have PVCs on routine electrocardiography. Uniform PVCs are probably benign, unless they are extremely frequent. However, more serious ventricular arrhythmias, especially when they are provoked by exercise testing and/or are associated with right ventricular hypertension at greater than 75% of systemic level should probably be treated. In this situation many centers would perform intracardiac electrophysiologic testing and assessment of various modalities of pharmacologic therapy, especially in patients who are symptomatic from their ventricular arrhythmias. Reoperation may be warranted if the cause of the residual right ventricular hypertension is amenable to surgical repair.

Other Long-term Considerations

Numerous followup studies of patients who have undergone tetralogy of Fallot repair have demonstrated that the vast majority of patients are functioning normally and do not consider themselves to be disabled. Most patients feel that they have normal exercise tolerance and exercise capacity has been demonstrated to be in the normal range in over 80% of patients by stress exercise testing.[181,182] Serial exercise testing has demonstrated no deterioration of exercise capacity in the majority of patients. Clearly this varies from one series to the next and is also dependent upon the percentage of patients with significant residual hemodynamic abnormalities that are included in each study.

Complete repair of tetralogy of Fallot eliminates neurologic complications such as brain abscess and cerebrovascular accidents that are possible in preoperative patients with hypoxia, polycythemia, and a right-to-left shunt. Patients who have had complete repair are still susceptible to infectious endocarditis since residual abnormalities are common, even though in most cases they are not hemodynamically significant. Thus, appropriate antibiotic prophylaxis against this problem is recommended for all patients throughout their lives.

The surgical management of tetralogy of Fallot has resulted in the likelihood that over 90% of patients with this lesion will survive to adulthood and lead active, healthy and productive lives. It is impossible to predict what will occur in the future but thus far, patients who have a good hemodynamic result from operations performed more than 30 years ago continue to show no signs of deterioration. The status of right and left function over the long-term are still of concern especially since the effects of coronary artery disease in a heart with a repaired congenital defect are unknown. Lastly, large numbers of patients are entering their child-bearing years and current data would indicate that the incidence of cardiac abnormalities in their offspring may be more than 15 times higher than in the general population. In this group, prenatal diagnosis by means of fetal echocardiography is strongly recommended. It is possible that these patients with repaired tetralogy of Fallot who are now surviving to adulthood will produce a new generation of children in whom the incidence of tetralogy of Fallot is much more frequent than in their parents' generation.

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CHAPTER 64

Absent Pulmonary Valve Syndrome

William W Pinsky

Congenital absence of the pulmonary valve leaflets is a relatively rare syndrome. Initial reports were described by Crampton in 1830[1] and Favell in 1842[2] with followup description by Cheevers in 1847[3] when he reported a syndrome of congenital heart defects that included absent pulmonary valve leaflets, ventricular septal defect, annular pulmonary stenosis, and dilatation of the main pulmonary artery and one or both of the pulmonary artery branches. Approximately 2 to 6% of patients described as having tetralogy of Fallot also have absence of the pulmonary valve leaflets.[4,5]

DEFINITION

In the absent pulmonary valve syndrome, there is either a complete absence of pulmonary valve leaflets or an uneven rim of rudimentary tissue found in the area of the pulmonary annulus. There is also stenosis of the annulus and perhaps also obstruction at the level of the infundibulum (Fig. 64–1). In the usual form of the syndrome there is overriding of the aorta, ventricular septal defect, and displacement of the right ventricular outflow tract to the left with an undeveloped infundibulum as seen in tetralogy of Fallot.[6] The most often recognized characteristic of the syndrome is the aneurysmal dilatation of the main pulmonary artery and its branches. There also may be stenosis at the origin of the pulmonary artery branches as well as arborization abnormalities. An uncommon but reported association of absence of the proximal portion of the left pulmonary artery exists,[7–17] and rarely, origin of one pulmonary artery from the ascending aorta.[18]

PHYSIOLOGY

Although the anatomy in the full syndrome is more similar to tetralogy of Fallot, the physiology is a combination of problems associated with left-to-right shunting and airway obstruction.[8,13,19] In early infancy, patients seem to divide themselves into two groups, one group with severe respiratory problems and one group with less severe problems. In the immediate newborn period, many of these patients are cyanotic, independent of their respiratory function. This is most likely because of the relatively high pulmonary resistance with an incompetent pulmonary outflow tract in association with a VSD. Characteristically the cyanosis abates as the pulmonary vascular resistance falls.[8,13]

The intracardiac shunting frequently becomes a net left-to-right shunt. Patients therefore have increased pulmonary blood flow. This increased flow in addition to the native dilatation of the pulmonary arteries may cause significant respiratory difficulties.[8,13] The dilated pulmonary arteries compress the large airway creating a ball-like effect. This effect may be compounded by enlargement of the left atrium, which further compresses particularly the left mainstem bronchus. There also may be intrinsic abnormalities to the integrity of the bronchioles causing further airway obstruction. Rabinovitch[19] thoroughly analyzed the lungs and vascularity in three post mortem patients using morphometric techniques. She found a bizarre pattern of hilar branching in addition to the expected central vascular airway problems. There were tufts that entwined and compressed the intrapulmonary bronchi. In addition, the histologic structure of the pulmonary arteries was abnormal. There were both decreased bronchial generations as well as impaired alveolar multiplication. It was these findings that led to

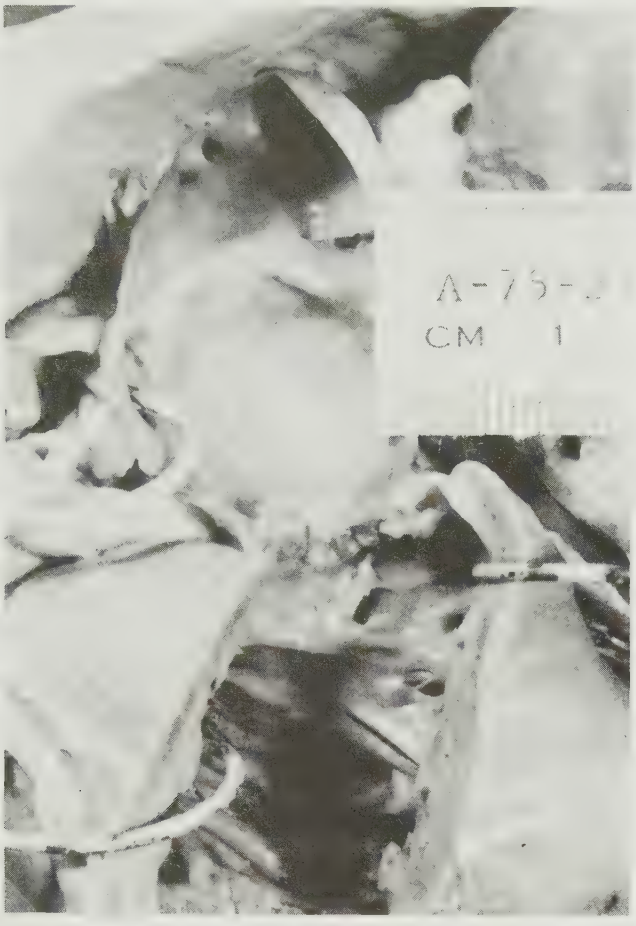

Fig. 64–1. Gross specimen of an infant heart opened from the right ventricular outflow tract into the main pulmonary artery. The hypertrophy of the right ventricle is demonstrated. Remnants of a pulmonary valve can be seen in the area of the pulmonary annulus. The main pulmonary artery is markedly dilated.

Rabinovitch's conclusion that some patients, even with relief of compression of the mainstem bronchi, still persist with severe respiratory dysfunction.

EMBRYOLOGY/FETAL CIRCULATION

The importance of the absence of the ductus arteriosus has been highlighted by Emmanouilides et al.[20] They reported four patients with this syndrome and absence of the ductus arteriosus. They feel there is a pathogenetic relationship between the lack of development of the ductus arteriosus and the pulmonary artery dilatation. It is felt that the lack of presence of the ductus arteriosus early in the fetus' life prevents the main outlet of the right ventricular circulation.[20] This would result in backwards blood flow through the pulmonary artery returning to the right ventricle and then passing to the lower resistance placental circulation from the left ventricle via the ventricular septal defect. Because the annulus is stenotic, poststenotic dilatation may also occur, further exacerbating the enlargement of the pulmonary arteries. This is a likely cause-and-effect relationship since the massive enlargement of the main pulmonary artery and its branches occurs as a prenatal event. There also may be a congenital weakness of the pulmonary arterial walls, although there has been no histologic evidence of this fact.[17,21] The right ventricular stroke volume is increased in utero due to the pulmonary insufficiency as well as the shunting through the ventricular septal defect.

Smith et al.[22] from the Mayo Clinic felt that the ductus was not involved as a primary problem. They hypothesized that in those patients where a ductus arteriosus was present, the aneurysmal dilatation of the pulmonary arteries and enlargement of the right ventricular cavity were exacerbated due to the increase in pulmonary arterial pressure in utero with diastolic runoff by way of the ductus arteriosus into the right side of the heart. This was disputed by Lakier,[8] who felt that the flow would be more prograde through the ductus to the systemic circulation, again because of the lower placental resistance.

The orientation of the right ventricular outflow tract and site of the VSD suggest a similarity with this syndrome and conotruncal maldevelopment as seen in tetralogy of Fallot.[6] In a review of their surgical cases, Calder et al.[18] felt most of the VSDs were consistent with a tetralogy location, however, they did have patients with deficiency in the conal septum that extended to a more anterosuperior direction, which differs from the classical tetralogy of Fallot. However, they felt that the constellation of defects still was very similar to that seen with tetralogy of Fallot.

ASSOCIATED ANOMALIES

Of the over 200 reported cases of absent pulmonary valve,[1–94] there have been only a few patients who had no associated cardiac anomalies.[22,35,46,54,69,75] Other than the tetralogy type of defect, other commonly associated anomalies include secundum atrial septal defect,[22,64,94] hypoplasia of the right ventricle,[46] double outlet right ventricle,[26,40,7,84] tricuspid valve atresia,[2,47,62,76] Marfan's syndrome,[36] endocardial cushion defect,[84] transposition of the great arteries,[19] Uhl's anomaly,[55] and aortic origin of one of the pulmonary arteries,[18,92] Additionally, DiGeorge syndrome[30,78] has been associated with this anomaly.

CLINICAL PRESENTATION

Because of the somewhat unusual constellation of defects and physiologic effects, infants may be referred to the cardiologist because of a heart murmur, cyanosis, "heart failure," respiratory failure or any combination thereof.[13] The murmur of absent pulmonary valve syndrome is unique, and other than aortic stenosis/insufficiency (e.g., aorticoventricular tunnel),[95] in the newborn it should not be confused with any other entity.

There may be cyanosis as a neonate when the pulmonary vascular resistance is relatively high and when there is relatively decreased compliance of the right ventricle decreasing the prograde flow through the pulmonary circulation with resulting right-to-left shunting through the ventricular septal defect. As the pulmonary vascular resistance decreases, then the cyanosis becomes less evident and more of a left-to-right shunt develops. Although many of these patients do not have the development of ductus arteriosus, it is interesting that infusion of PGE_1 may cause improvement in their cyanosis. This most likely is due to the prostaglandin's effect in decreasing vascular resistance[96] as opposed to opening a "nonexistent" ductus arteriosus.

"Congestive heart failure" as evidenced by increased respiratory rate, rales, gallop, and evidence of increased pulmonary blood

flow will manifest itself as the pulmonary resistance drops. Not all patients with this syndrome will have these findings as the pulmonary annular stenosis may restrict enough left-to-right shunting to give a "balanced picture." Patients who do exhibit signs of increased left-to-right shunt may have this shunting decrease as the infundibular stenosis develops over time.

Presentation with significant respiratory insufficiency is frequently the reason for referral. These patients have air trapping secondary to the bronchial and bronchiolar compression from the enlarged aneurysmal pulmonary arteries and pulmonary arterioles as described earlier.[8,13,19] This can be a diffuse process or it can be more segmental. On examination one can find evidence for adequate air intake but expiration is greatly diminished. Lungs become hyperresonant with potential shifting of the cardiac structures.

PHYSICAL EXAMINATION

In patients without severe respiratory involvement there will be minimal cyanosis.[13] The degree of overriding of the aorta and amount of annular stenosis are significant determinants in the degree of cyanosis. In practicality, the annular stenosis and infundibular hypertrophy generally are not as severe as in the standard tetralogy of Fallot; therefore the patient's cyanosis is less prominent in this syndrome. The chest examination should be unremarkable except for perhaps slightly increased resonance. Breath sounds should be unremarkable. The precordial examination will demonstrate an active right ventricular impulse at the left lower sternal border commensurate with the degree of right ventricular volume and pressure overload. Depending on the degree of left-to-right shunting, the left ventricular impulse may have increased activity although the apex is generally not displaced. The first heart sound is normal and the second will be single and increased. There is a high-pitched systolic ejection murmur, secondary to the annular and infundibular stenosis, that is maximally located at the third left intercostal space although it will radiate through the pulmonary distribution, that is, to the right chest anteriorly and to both sides of the back. A typical low-pitched decrescendo diastolic murmur of pulmonary valve insufficiency will be heard in the third left intercostal space. This creates the typical to-and-fro murmur of this entity.[97]

In patients with severe bronchial compression, their cyanosis is more dependent upon the degree of respiratory distress.[8,13,19] These patients may have a significant amount of air hunger secondary to trapping. Although the pCO_2 will increase first, there can be a significant decrease in the pO_2 as respiratory failure progresses. There is generally hyperinflation with increased resonance on percussion of the chest, which can be diffuse or segmental depending upon the distribution of involvement. Breath sound alteration will track the degree of lung involvement. The cardiac findings will be similar to that found in patients without significant respiratory problems.

NONINVASIVE TESTING

Chest radiographs indicate a range from a normal to mildly enlarged cardiac silhouette. Enlargement of the cardiac silhouette is generally due to enlargement of the right ventricle. Typically there is marked dilatation of the main pulmonary artery as seen on chest radiograph with prominence of the pulmonary artery branches seen centrally. Depending upon the amount of left-to-right shunting, the left mainstem bronchus may be upturned as the left atrium enlarges.[8] Relative to the amount of respiratory involvement, there is hyperinflation secondary to bronchial obstruction (Fig. 64–2). In severe forms of air trapping, there may actually be herniation of a lobe. This may result in mediastinal shift. One should note the position of the trachea to help in identifying a right-sided aortic arch, found in this syndrome similar to some patients with tetralogy of Fallot.

The electrocardiogram typically demonstrates right axis deviation and right ventricular hypertrophy secondary to both right ventricular pressure and volume overload states. There may be associated left ventricular hypertrophy in those individuals with significant right-to-left shunting. There also may be right atrial enlargement usually on the basis of decreased right ventricular compliance.

Echocardiography can be diagnostic for this syndrome. As suggested by Cheatham et al.[34] and further described by de Albuquerque et al.,[85] in addition to the overriding large posterior great artery with subaortic ventricular septal defect, the right ventricular outflow tract will be patent and a narrow pulmonary annulus noted. The pulmonary valve will be poorly visualized.[66] The main pulmonary artery will be identified as quite enlarged as will one or both of the branches. There will be evidence of right ventricular volume overload by an enlarged right ventricle and paradoxical septal motion. Doppler interrogation will demonstrate turbulent flow across the right ventricular outflow tract with a significant

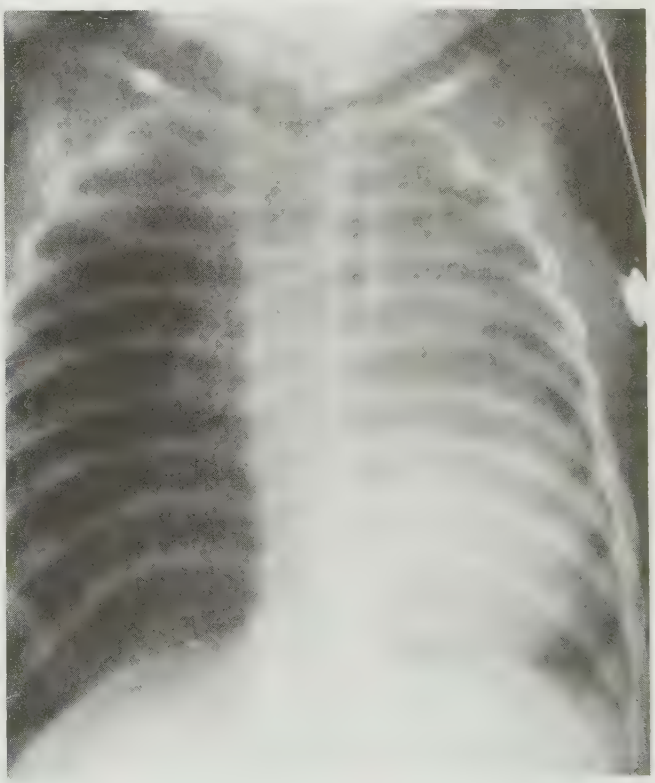

Fig. 64–2. AP chest roentgenogram of an infant. Note flattening of the diaphragms indicative of the hyperinflation secondary to air trapping.

gradient calculated. In addition, pulmonary insufficiency is displayed by diastolic flow through the pulmonary artery back into the right ventricular outflow tract. An important observation is that ductus arteriosus flow will not be identified. Obviously those instances where the absent pulmonary valve is in association with other intracardiac type of defects, those findings will be present in addition to the Doppler findings of pulmonary insufficiency and right-sided enlargement.

INVASIVE TESTING

In patients with the usual syndrome, there is equalization of the pressures between the ventricles due to the large ventricular septal defect. The gradient across the RV outflow tract will depend upon the amount of narrowing in the infundibular and annular areas. The diastolic pressure in the pulmonary artery approaches zero indicating the lack of restriction of flow back into the right ventricle due to severe pulmonary insufficiency. There may be a gradient to either pulmonary branch depending upon stenosis of those areas. Even with a left-to-right shunt, the pulmonary vascular resistance is generally normal. Increased right atrial pressure indicates some loss of compliance of the right ventricle due to its volume and pressure overload states. Left ventricular end diastolic pressure and atrial pressure will reflect the increased degree of left-to-right shunting as the QP/QS increases. Oxygen saturations indicate a normal mixed venous oxygen saturation with a step up in saturation in the right ventricle and pulmonary arteries. Depending upon the degree of override of the aorta, there may be some arterial desaturation as well. Right ventricular angiography reveals the typical "Mickey Mouse ears" appearance of the dilated main pulmonary artery and its branches (Fig. 64–3). The right ventricular injection utilizing cranial oblique views visualizes the origin of the pulmonary arteries and their distribution to rule out any localized areas of stenosis. Also, the degree of right-to-left shunting can be identified angiographically. A contrast injection in the main pulmonary artery will characterize the degree of pulmonary insufficiency, as well as delineate areas of vascular crowding secondary to air trapping. Left ventricular angiography, again using cranial oblique views, delineates the exact site of the defect in the ventricular septum. In the usual syndrome, there are not multiple ventricular defects; however, variations can be expected. Because of the concern for coronary artery distribution abnormalities in those with tetralogy of Fallot, it is important to identify the course particularly of the left anterior descending coronary artery before planning intracardiac repair.

NATURAL HISTORY

Those patients with severe bronchial obstruction will develop respiratory symptoms, sometimes as early as the early neonatal period.[13,20,27,41,53,54,61,91] In other cases, symptoms may develop later in the first month of life. Generally these symptoms are exacerbated by any type of respiratory infection. As in other forms of congenital heart disease, infection with respiratory syncytial virus can be very serious. Frequently the respiratory symptoms will overshadow the cardiac problems from the left-to-right shunt. As the airways increase in size and integrity, the respiratory symptoms will tend to regress. However, this cannot be expected until at the earliest 6 to 9 months of age. Frequently the respiratory status will stabilize after age 1.[8,13] These patients may have significant growth failure secondary to decreased caloric intake as well as caloric usage primarily on the basis of their respiratory failure.

Those patients with less severe bronchial compression act more like a patient with "pink tetralogy of Fallot." Different from

Fig. 64–3. Right ventricular angiogram in a cranial/LAO position. This demonstrates a narrowed annulus. There is marked dilatation of the main pulmonary artery and its branches.

patients with tetralogy of Fallot who have increasing cyanosis with age,[98] these patients do not become more cyanotic. They may have some "heart failure" with related symptoms. Their respiratory symptoms are mild at most and only require treatment in unusual circumstances. As in other patients with significant left-to-right shunts, they also may have growth failure.

THERAPEUTIC APPROACH

In patients with severe bronchial obstruction their medical treatment needs to be directed toward their respiratory function.[25,13] Specific therapy to improve ventilatory function should be much more effective in relieving symptoms in this group than anticongestive measures. It is sometimes necessary to mechanically ventilate those infants who develop respiratory acidosis with significant hypercarbia. However, it is important to ventilate these patients only in extreme instances and with minimal settings. Once one makes such a patient ventilator dependent with positive pressure, it is very difficult to wean from the support. Continually pumping air into the lungs without adequate expiration may only exacerbate the air trapping. A respiratory therapy program in the hospital including nebulization of agents to reduce secretions and dilate the airway frequently can be successful. Treatment of any ongoing respiratory infections likewise is necessary. Arensman et al.[25] described successful experience of positioning patients with severe respiratory problems in a semiprone position (patient lying with head elevated) to maintain their airway patency. Utilizing a type of "Herbst board," they found their patients could be treated successfully medically. They recommend this type of approach because of the reported high surgical mortality in young infants with this syndrome and respiratory distress.

Patients with more minor symptoms will also benefit by a preventive respiratory program. This would include early treatment of respiratory infections sometimes even necessitating a home inhalation program as is used with patients with chronic asthma or cystic fibrosis. The symptoms of left-to-right shunting should be treated in the usual manner with decongestive measures and nutritional support.

There is no uniform consensus to the surgical approach to these patients.[19] Patients with this syndrome have undergone palliative plication of the aneurysmal pulmonary arteries in infancy to help relieve the symptoms.[23,25,41,61,62,77] However, these patients frequently continue to have respiratory distress even after this procedure is accomplished. This may be due to the abnormality of the pulmonary arterioles as suggested previously by Rabinovitch.[19] Certainly, plication without repair of the intracardiac defects has not been very successful.[19] Other individuals have suggested banding of the main pulmonary artery to reduce pulmonary arterial flow thus decompressing the pulmonary artery circulation and left atrium.[68,70] An extension of this technique would be to ligate the main pulmonary artery and then perform a systemic arterial to pulmonary artery anastomosis.[29,53] Patients would then have further intracardiac repair at a later time. Some continue to stress the need for "aggressive" medical therapy and surgical therapy during infancy only when forced because of poor progress of the respiratory situation.[25,13]

Further controversy exists whether it is necessary to insert a prosthetic valve in the pulmonary location. We[13] reported a series where prosthetic pulmonary valves were not inserted and appeared to have good long-term outcome. This included two patients who went on to carry pregnancies successfully to term. Others feel that insertion of a prosthetic valve will lower the volume overload state to the right side of the heart thus reducing the pulmonary artery dilatation.[18,41,52,60,63] Although this is theoretical, this has not been demonstrated to be a necessary cause-and-effect relationship. The insertion of a prosthetic valve adds to the risk of surgery and long-term to the potential complications with mechanical valves and bioprostheses.

OUTLOOK

Patients who have undergone successful intracardiac repair generally have an improvement in their respiratory situation so that does not continue to be a limiting factor in their life. However, one should be aware that successful anatomic repair does not dictate relief of respiratory symptoms in the early postoperative period. In the patients with the usual syndrome, their long-term outlook should be similar to patients with tetralogy of Fallot who have had intracardiac repair and have pulmonary valve insufficiency. These patients, similar to the postoperative tetralogy, need to be observed for the development of arrhythmias and ventricular dysfunction.

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CHAPTER 65

Pulmonary Valve Atresia with Intact Ventricular Septum

Donald A Riopel

Pulmonary valve atresia with intact ventricular septum (PA-IVS), also known as pulmonary valve atresia with normal aortic root, is a lesion that consists of varying degrees of hypoplasia of the right ventricle and tricuspid valve. Early writers on the subject were Hunter,[1] Lordat,[2] Hare,[3] and von Rokitansky.[4] The clinical course of very severe hypoplasia of the right ventricle can be almost as devastating as that of severe hypoplasia of the left heart. Although a simple surgical procedure in the neonatal period may save patients with severe hypoplasia of the right ventricle, many such infants die in the first year of life from complications. On the other hand, infants with moderate or mild hypoplasia have a more favorable clinical course. There has not always been unanimity among clinicians about the proper timing and sequence of medical and surgical procedures for this defect, but a common approach appears to be evolving. Possibilities using autogenous muscle are being investigated for the future.

INCIDENCE

The defect accounts for 1 to 3% of cardiac lesions.[5–7] It is estimated to occur in 0.1 to 0.4 per 10,000 births.[8] No distinct sexual preference occurs, although the defect is stated to occur slightly more in boys. A clustering of cases has been reported.[9]

ETIOLOGY

Pulmonary valve atresia can be viewed as the most severe form of valvar pulmonary stenosis. The embryologic origin of the defect has been difficult to demonstrate or to reproduce. At stage 15 of embryological development, four mounds of endocardial cushion tissue are present in the outflow channel of the developing heart tube. There are two large lateral cushions and two smaller cushions in the anterior and posterior positions. Each of the larger lateral cushions is subdivided to form two juxtaposed cusps, one in the pulmonary artery and the other in the aorta. These juxtaposed cusps result in the eventual formation of the thin aortic and pulmonary valve cusps.[10] Embryologic maldevelopment of the endocardial cushions should result in abnormalities of both semilunar valves. However, the presence of abnormalities in one valve without abnormalities in the other semilunar valve suggests that the etiology occurs after the valve cusps have formed.[11] Developmental abnormalities in this area of the conal septum would theoretically also result in deficiencies of the ventricular septum, which usually do not exist in isolated valvar pulmonary stenosis or atresia.[12] Kutsche and Van Mierop[13] postulate that in PA-IVS, atresia of the pulmonary valve very likely occurs sometime after cardiac septation has been completed. The majority of the cases have well-developed fused pulmonary cusps with the typical triradiate appearance. The pulmonary artery diameter is almost normal in size in PA-IVS,[14] while in pulmonary atresia with ventricular septal defect (PA-VSD) the pulmonary arteries are generally small and underdeveloped.[13] The patent ductus arteriosus has a more normal structure and horizontal course in patients with PA-IVS, while it is sigmoid, tortuous, and with a downward course in PA-VSD.[13,15] These findings suggest that in fetuses with PA-IVS, there is at one time normal fetal blood flow from the pulmonary outflow tract through the pulmonary artery and ductus arteriosus to the descending aorta, while in PA-VSD, the direction of blood flow is always reversed through the ductus, suggesting

earlier atresia of pulmonary outflow. A fetal inflammatory process has long been proposed as a cause of pulmonary stenosis or atresia with intact ventricular septum.[16–19] The association of pulmonary artery obstruction with rubella infections[20] serves to bolster this hypothesis.

PATHOLOGY

Edwards and associates[21] describe the condition as one that consists of (1) complete obstruction of the pulmonary valve, (2) two distinct ventricles, and (3) a patent tricuspid orifice guarded by a valve. The pathological anatomy of PA-IVS is also well described in series published by Greenwold and associates,[22] Davignon and associates,[23] Freedom and associates,[5,24] Zuberbuhler and Anderson,[14] Bull and associates,[25] and Kutsche and van Mierop.[13]

The pulmonary valve tissue is a membrane, in most cases with fused commissures depicted by raphae and with three formed cusps. The valve was described thus in 60 of the 75 cases reported by Freedom and Keith.[5] In that series, only two valves were bicuspid, and in three instances no valve tissue was present. In Zuberbuhler and Anderson's[14] series, three cases had no pulmonary valve leaflets; in the remaining 23 cases, two types of atretic pulmonary valves were noted. Both types had commissural ridges. In one type, the ridges met in the center (a feature usually associated with severe infundibular atresia), while in the other type, the ridges were present only at the periphery of the membranous pulmonary valve with the center bulging and smooth. In only one case was the pulmonary valve bicuspid, and in one it was quadricuspid. In the series reported by Kutsche and van Mierop,[13] 15 of 20 specimens had three fused cusps.

All series reported a slightly reduced but well-formed, near-normal-sized pulmonary annulus and main pulmonary artery, indicating the probable presence of normal intrauterine blood flow through these structures and the ductus arteriosus, since the ductus had more normal anatomy (supra vidae).

The right ventricular cavity varies in size from tiny to larger than normal, although it is smaller than normal in the majority of cases. In 1956, Greenwold and associates[22] reported 12 cases of PA-IVS; six of the patients had a tiny ventricle, and six had a large ventricle. Differences in electrographic and radiographic patterns were emphasized. Although all patients died, Greenwold and his colleagues concluded that perhaps patients with larger ventricular cavities might benefit from surgery. In 1961, Davignon and associates[23] examined 20 cases of PA-IVS and classified them into two types depending on the size of the ventricle. Type I was described as having a tiny right ventricular cavity, and Type II as having a normal-sized or large right ventricular cavity. However, most published reports emphasize that there is a continuum of right ventricular cavity size. Freedom and colleagues' review of 60 cases[24] classified the right ventricle as markedly underdeveloped in 40%, moderately underdeveloped in 30%, mildly underdeveloped in 10%, normal in 6.5%, and enlarged in 13%. As surgical results were reported, it seemed that some right ventricular cavities could become larger after surgery, a finding that prompted a revised classification of the right ventricle by Bull and associates.[25] This classification was based on the tripartite approach of Goor and Lillehei,[26] who defined a sinus (inlet) portion, incorporating the tricuspid valve apparatus, a trabecular portion lying beyond the insertion of the papillary muscles of the tricuspid valve toward the apex, and a conus (infundibulum) leading to the pulmonary valve. In the report by Bull and associates, all cases of PA-IVS had an inlet portion of the right ventricle, since by definition the tricuspid valve is patent in all of them. Some cases had no trabecular cavity, while others lacked both infundibular and trabecular portions. No patient lacked only an infundibular portion. These authors postulate that variations in muscular hypertrophy rather than hypoplasia account for the presence or absence of various parts of the right ventricle and for the differences in cavity size. The tripartite classification allowed de Leval and colleagues[27] to plan their approach to surgical therapy and to predict prognosis. Arom and Edwards[28] examined the hearts from 18 infants with PA-IVS, paying particular attention to certain muscle bundles of the infundibulum. They felt that specific muscle bundles were consistently related to certain pulmonary valve cusps and that severe hypertrophy of these muscle bundles could completely obliterate the infundibular portion of the right ventricle, isolating the pulmonary valve membrane from the sinus of the ventricle. They concluded that in some ventricles with a narrow infundibulum, only the anterior pulmonary cusp was the part of the membrane in continuity with the infundibulum and that valvotomy should be performed through this portion only.

In 1926, Grant[29] described a case of pulmonary atresia in which there were communications between the ventricle and the coronary artery system via myocardial sinusoids. Since then, several authors have described these unique channels morphologically[23,30–32] and angiographically.[33] Sinusoids have also occurred in some cases of left ventricular outflow obstruction.[34,35] The sponge-like musculature of the embryologic heart muscle is supplied with blood from the intertrabecular spaces and sinusoids. Later, coronary veins develop and communicate with the sinusoids. The coronary arteries develop later and anastomose with the veins. As the myocardium becomes more muscular, the venous communications with the cavity of the ventricles become atretic. At the time of pulmonary valve development, the blood supply to the heart is still derived from its lumen, and if the valve does not develop normally, the elevated pressure in the right ventricular cavity may keep open the sinusoids and venous communications will persist. These fistulous communications seem to be most prominent with small hypertensive right ventricles, occurring in 8 to 55% of reported cases.[36,37] The flow through the coronary arteries can be retrograde (toward the aorta) or bidirectional.[38] Communications are more often with the left anterior descending and left coronary artery than with the right coronary artery. These sinusoids provide an egress of blood from the right ventricular cavity, where forward flow is not possible. Lenox and Friner report a case in which the proximal connections between the aorta and coronary arteries were absent.[39] The coronary arteries undergo a variety of changes resulting in beading, nodularity, and endarteritis, compromising oxygen transport and leading to ischemia of the myocardium.[37] Fibroelastic changes often occur in the right ventricular endocardium, especially at the orifices of the sinusoids.[35]

The tricuspid valve, by definition, is patent in all cases of PA-IVS. Davignon and associates[23] described the valve to be smallest in his type I defects, those with the smallest right ventricles. In the type II defects, the valve was larger, and there was evidence of valvar incompetence. The relationship of the size of tricuspid valve to right ventricle has also been described in other case re-

views.[5,14,24,40] The size of the tricuspid orifice and valve ring appears to be proportional to the size of the right ventricular cavity, although some exceptions were found.[14] In general, the tricupsid valve annulus and orifice tend to be small, and the leaflets tend to be dysplastic, sometimes resembling Ebstein's malformation. The leaflet margins are often rolled and thickened and sometimes attached directly to the small papillary muscles with no intervening chordae. The deformity of the tricuspid valve results in varying severity of stenosis or insufficiency. The size of the tricuspid valve is important in the prognosis of this defect and will be discussed later in this chapter.

The right atrium varies in size depending on the degree of tricuspid insufficiency or stenosis and also depending on the presence of a communication between the right and left atrium. A markedly dilated foramen ovale provides a communication between the right and left atria in most cases, a true secundum defect being present in only 20% of cases.[41] No cases of ostium primum defects in PA-IVS have been reported,[34] but bulging of the primum portion of the atrial septum can obstruct the mitral valve.[42] Severe restriction of the atrial septal communication may be present in 5 to 10% of cases.[34]

Pulmonary veins, the left atrium, and the mitral valve are usually normal. The left ventricle is dilated and hypertrophied. The aortic valve also is usually normal, but some cases of aortic valve stenosis have been described.[43] The aortic arch is left-sided when situs solitus is present.

PHYSIOLOGY

Fetal

With no outlet of the right ventricle, in the fetus with PA-IVS, all systemic venous blood is directed to the left side of the heart through a communication in the atrial septum. Therefore blood flow through the left atrium, mitral orifice, left ventricle, aortic orifice, ascending aorta, and aortic isthmus is increased in comparison to that of the normal fetus. In fact, the total cardiac output must be carried by the left heart, whereas only about 33% of the output is normally carried by the left side.[44] This results in a larger than usual left heart, a larger ascending aorta, and a normal or large aortic isthmus. Flow through the ductus arteriosus is reversed and carries only 8 to 10% of cardiac output, while in the normal fetus, 55 to 60% of cardiac output flows through this structure from main pulmonary artery to descending aorta. As was previously mentioned, the ductus arteriosus in PA-IVS is horizontal and fairly large, suggesting early normal fetal flow through it before the pulmonary valve becomes atretic.

Postnatal

Systemic venous blood enters the right atrium from the vena cavae, and some enters the right ventricle through the patent tricuspid valve; the actual amount depends on the size of the valve and the right ventricle. With no exit possible through the pulmonary valve, the blood must be returned to the right atrium through an insufficient tricupsid valve. Eventually, almost all the systemic venous blood must cross the atrial septum through the foramen ovale or atrial septal defect. Since the communication between atria is necessary before birth, it is usually adequate after birth but may become inadequate several weeks or months later when pulmonary blood flow is better established. In the left atrium, all systemic venous blood mixes with pulmonary venous blood, and systemic arterial blood oxygen saturations depend on the amount of pulmonary blood flow, which in turn depends on the size and patency of the ductus arteriosus. As the ductus undergoes a natural tendency to close, oxygen tension decreases and symptoms of hypoxia occur.

Coronary blood flow through the right ventricular myocardium, even in infants without sinusoid communications, is abnormal. In normal children, blood flows through the right coronary artery system during both systole and diastole, since right ventricular pressures are low throughout the cardiac cycle. However, in infants with PA-IVS, the extremely high pressure in the right ventricle reduces coronary flow, which results in chronic ischemic changes especially in the subendothelial layers and may account for the subendocardial fibrosis of the right ventricle seen in many of these patients.

With the presence of communications between the coronary artery system and the right ventricle via right ventricular sinusoids an intracardiac right-sided circular shunt is formed,[31] which allows venous blood to return to the right atrium without passing through the systemic capillary bed. The pathway of the shunt is from right ventricle to intramyocardial sinusoid, coronary artery, coronary vein, coronary sinus (or thebesian vein), right atrium, and again to right ventricle. The abnormal physiology affects left coronary blood flow and is clinically important when surgery is contemplated.[32]

CLINICAL PRESENTATION

Most infants presenting with PA-IVS are born of a term gestation, have not had growth retardation in utero, and are vigorous. Signs of cyanosis occur variably from a few hours to several days after birth and depend on ductal flow. The cyanosis may be intermittent and associated only with the stress of feedings or may be sudden and severe because of sudden closure of the ductus arteriosus. Infants with very severe cyanosis also have accompanying acidemia and deep compensatory respirations in an attempt to correct the metabolic acidemia. The type of respirations are those of hyperpnea rather than the labored respirations of the infant with the respiratory distress syndrome. Hypoxemia, acidemia, or hypoglycemia can, singly or in combination, lead to seizure activity.

In the symptomatic infant, there is deep cyanosis of the mucous membranes and nailbeds with paleness of the skin secondary to a decrease in cardiac output and peripheral vasoconstriction. The point of maximal impulse is prominent and is located substernally. Hyperpnea is present, and on auscultation of the lungs, no rales are heard. Cardiac auscultation may reveal only the single second heart sound of aortic closure with no murmur, especially if the right ventricle is very small and there is no significant tricuspid insufficiency. If the right ventricle is normal or large in size and there is tricuspid insufficiency, then a long systolic murmur is heard along the lower left sternal border, often with diastolic filling sounds. Rarely is a continuous murmur heard. The liver may be engorged and pulsatile because of passive congestion. Pulses may be diminished.

LABORATORY FINDINGS

Electrocardiogram

The electrocardiographic (ECG) findings of PA-IVS vary depending on the anatomy of the defect and are well described in several series.[45–49] The rhythm is sinus with normal ECG intervals. The P wave is slightly peaked in cases of small right ventricle with little or no tricuspid insufficiency but tall and peaked in cases with considerable tricuspid insufficiency. The P-wave frontal plane axis is normal. The QRS frontal plane axis tends to be in the lower left quadrant or up to $+120°$ in cases of small right ventricle, while it is usually very rightward (greater than $+120°$) in cases with normal or large right ventricles. In severely hypoplastic right ventricles, the R/S ratio in the horizontal plane favors the posterior forces, a finding that suggests absent or diminished right ventricular forces (Fig. 65–1). With a large right ventricle, anterior forces predominate, and criteria for right ventricular hypertrophy are fulfilled. The T wave is usually normal except in cases in which there is ischemia of either the right or left ventricle, in which case discordant T waves are seen, and ST changes of strain are present.

Radiologic Findings

Chest roentgenograms in PA-IVS vary with the anatomic type.[5,50,51] In cases with a tiny right ventricle and little or no tricuspid insufficiency, the heart is normal in size. The main pulmonary artery segment may be deficient or normal, and the overall silhouette may be surprisingly normal. The vascularity is reduced or normal, depending on the patency of the ductus arteriosus. The aortic arch is leftward; a right arch is more often associated with PA-VSD. In cases in which the right ventricle is normal or large with tricuspid insufficiency, the overall heart size is increased, and the enlarged right atrium gives considerable convexity to the right heart border. Since tricuspid insufficiency has been occurring in utero, the right atrium can be huge at birth with an immense cardiac silhouette resembling that of Ebstein's anomaly.

Echocardiography

Although cardiac catheterization and angiography are the most definitive methods of evaluating the anatomy and physiology of PA-IVS, modern echocardiography approaches the same degree of exactness by a noninvasive method. M-mode evaluation of this defect[52,53] has been largely surpassed by the use of two-dimensional standard and color Doppler.[54–56] Four-chambered views allow visualization of the relative sizes of the ventricles and atria (Fig. 65–2a). The presence and size of an atrial septal opening can be visualized and measured. Bulging of the atrial septum into the left atrium should indicate a restrictive opening in the septum.[42] The patency and size of the tricuspid valve will be clearly seen, and function of the ventricles can be evaluated. In short-axis views, the pulmonary valve membrane can be seen as well as the size of the valve ring. The size of the main pulmonary artery and the distance of the proximal main pulmonary artery from the distal right ventricular outflow tract is measurable. Color Doppler echocardiography will show the presence and degree of tricuspid insufficiency (Fig. 65–2b). The right-to-left shunt across the atrial septum and the flow into the main pulmonary artery through the ductus can also be appreciated by color Doppler. Following the surgical relief of pulmonary atresia, the flow and pressure gradient across the pulmonary orifice and right ventricular pressure can be estimated by continuous-wave Doppler.

Cardiac Catheterization

The diagnosis of hypoplasia of the right heart is made from use of the previously mentioned laboratory tools, especially ultrasound. However, cardiac catheterization and angiography remain necessary for visualizing all the details of the anatomy, measuring pressures, and performing necessary interventional procedures. Since many of these infants require balloon septostomy,[57] it can be performed in the newborn period without the use of transseptal equipment or blade catheters. Sinusoidal communications with the coronary artery system are best evaluted by angiography.

The use of prostaglandin E_1 to dilate the ductus arteriosus[58] and

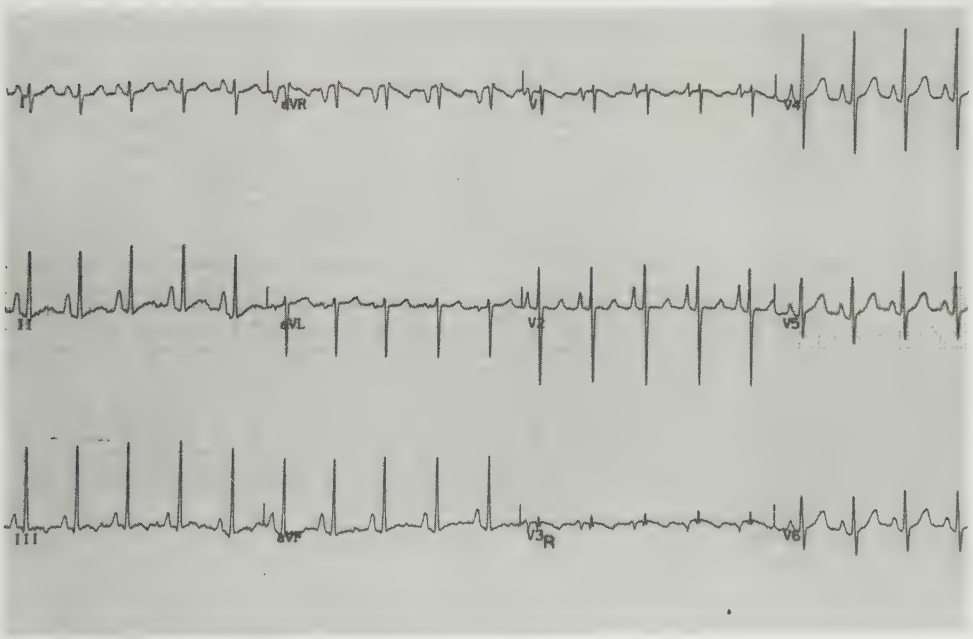

Fig. 65–1 Twelve-lead electrocardiogram of a neonate with PA-IVS and small right ventricle. Note the tall, peaked P waves in lead II and decreased anterior forces in lead V_1.

Fig. 65–2. (a) Two-dimensional echocardiogram in four-chambered view showing the very small right ventricular cavity and severe hypertrophy of right ventricular muscle. (b) Color Doppler echocardiogram showing severe tricuspid insufficiency in the same child.

maintain pulmonary blood flow in these infants has greatly enhanced the safety of catheterization. The infant will change from blue, pale, and acidemic to pink and well perfused within minutes of starting an infusion of prostaglandin E_1 at the rate of 0.05 to 0.1 μg/kg/min. Lower doses may be used with good results. The infusion is effective when given through any vessel including peripheral veins, umbilical vein, or artery. The improved state is maintained as long as the prostaglandin is being infused. Because of possible side effects from prostaglandin such as apnea, seizures, rash, and fever, the infusion should not be prolonged unnecessarily. Prostaglandin will allow cardiac catheterization to proceed less hurriedly at a more opportune time and will also allow some time for the infant to recover from the catheterization before surgery.

Usually, only a venous catheter is necessary for catheterization. Since most infants will have an umbilical artery monitoring catheter, the femoral artery rarely has to be violated. The venous catheter course will be from inferior vena cava to right atrium and thence to the right ventricle. Because of hypoplasia of the tricuspid orifice, the right ventricle may be difficult to enter, and the infant may be thought to have tricuspid atresia. An angiogram in the right atrium will differentiate this, but with prior echocardiography this differentiation should not be necessary. The pulmonary artery is not accessible from the right ventricle. The left atrium is entered through a patent foramen ovale or atrial septal defect. Manipulation into the left ventricle from the left atrium is possible with the use of either a balloon-directed catheter or a J-wire through an end-hole catheter or with the use of a tip deflector inside a closed-tipped angiographic catheter. Hemodynamic data have been summarized in a number of publications.[5,46,47,51] Right atrial pressures are elevated with tall A waves of 15 to 20 mm Hg and mean pressures of 3 to 18 mm Hg (Fig. 65–3). Left atrial pressures are lower by 2 to 3 mm Hg. Right ventricular systolic pressure in those patients with a small right ventricle and very little tricuspid insufficiency have suprasystemic values with a peaked configuration of the pressure curve (Fig. 65–4). Right ventricular systolic pressures may achieve levels of 200 mm Hg but are usually between 100 and 150 mm Hg. Right ventricular end-diastolic pressures will also be elevated, equal to right atrial levels. In those right ventricular chambers with diminished contractility, the systolic pressures can be quite low. The pressures may also be normal

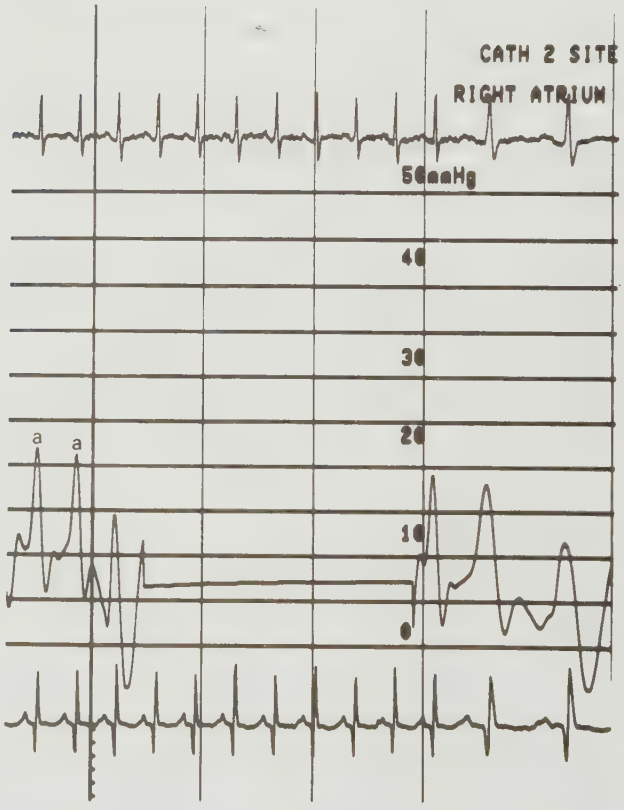

Fig. 65–3. Right atrial pressure tracing from a neonate with PA-IVS showing tall A waves and elevated right atrial pressures.

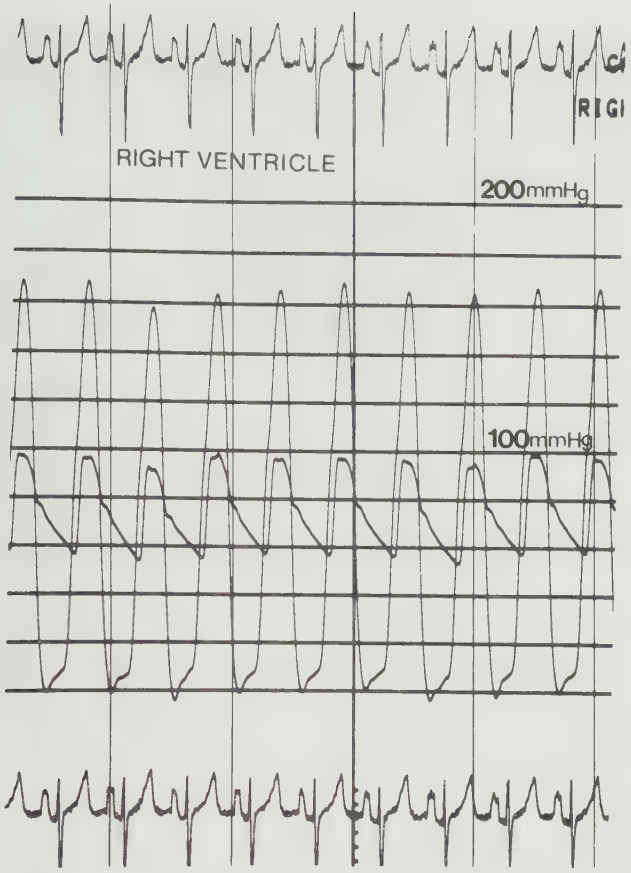

Fig. 65–4. Right ventricular pressures with simultaneous aortic pressures in a neonate with PA-IVS. The right ventricular pressures are peaked and suprasystemic.

or low in cases with large right ventricles and tricuspid insufficiency. Left ventricular pressures usually have normal newborn values unless there is severe hypoxemia, acidemia, and hypoglycemia, all of which decrease contractility and result in low systolic and high end-diastolic pressures. Oxygen saturations are invariably very low in infants who are not being given prostaglandins. Caval and right atrial saturations are often below 30%. Pulmonary venous saturations should be normal. Left atrial saturations are variable because of streaming, and left ventricular saturations reflect arterial saturations that are decreased to an average of about 44%. Because of the large intracardiac right-to-left shunt, administration of oxygen increases systemic saturations very little if any. Arterial blood gases in infants not on prostaglandins will have a low pH, a very low pO_2, often below 20 mm Hg, and a pCO_2 that is somewhat low with a negative base excess. In infants who are receiving prostaglandins, the saturations in all chambers might be surprisingly near normal with very little systemic desaturation. Arterial blood gases in these infants might also approach normal values.

Balloon septostomy should be performed before the end of the catheterization to ensure a good communication between the atria.

Angiography

The preferred locations for angiography are in the right ventricle and in the left ventricle or aorta. An injection in the right ventricle will establish the diagnosis, will show the size of the right ventricle, and will allow classification into the standard type I or II of Greenwold and associates[22] or into the tripartite classification of Bull and associates.[25] Communications with the coronary artery system via myocardial sinusoids may be demonstrated (Fig. 65–5), as well as the degree of tricuspid hypoplasia and insufficiency (Fig. 65–6). Right ventricular volumes are estimated angiographically,[36,59,60] and tricuspid annular size is measured[61] (Fig. 65–7); both are used clinically to plan surgical procedures. Differentiation between functional and structural pulmonary atresia is accomplished during aortography by the observation of pulmonary insufficiency in cases of functional atresia.[62] An important factor in predicting the possibility of establishing continuity between the right ventricle and pulmonary artery is the distance between the distal right ventricular outflow tract and the proximal

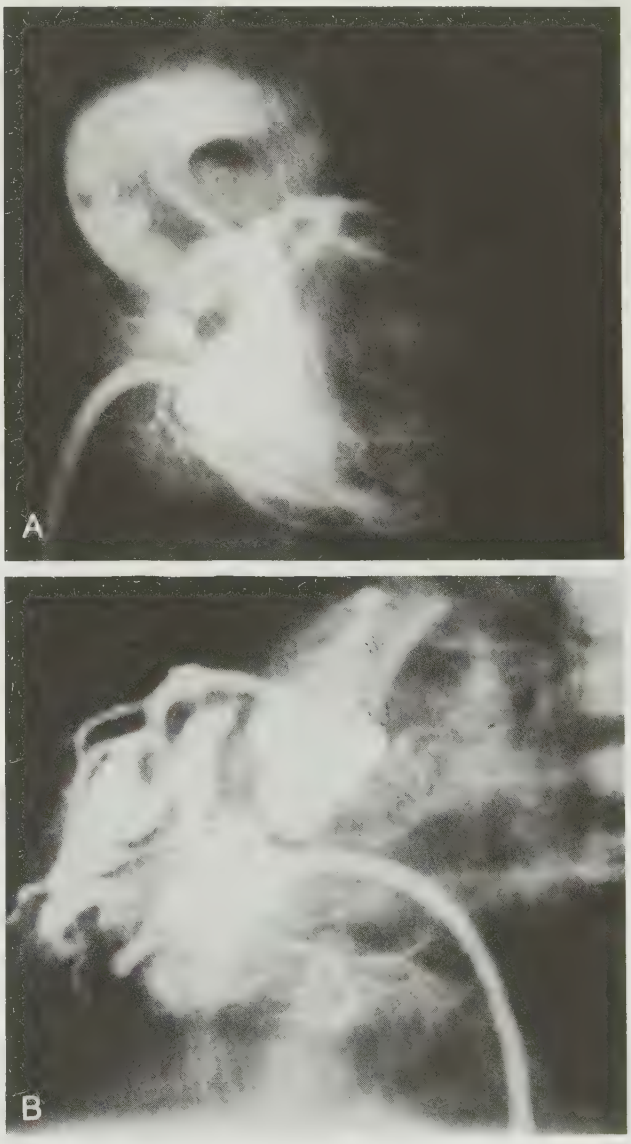

Fig. 65–5. (a) Anteroposterior and (b) lateral views of a right ventricular angiogram in a neonate with PA-IVS showing a very hypoplastic right ventricle and large right ventricular sinusoids communicating with the aorta via the coronary artery circulation.

Fig. 65–6. Right ventricular angiogram in a neonate with PA-IVS revealing a hypoplastic tripartite right ventricle, severe tricuspid insufficiency, and a large right atrium.

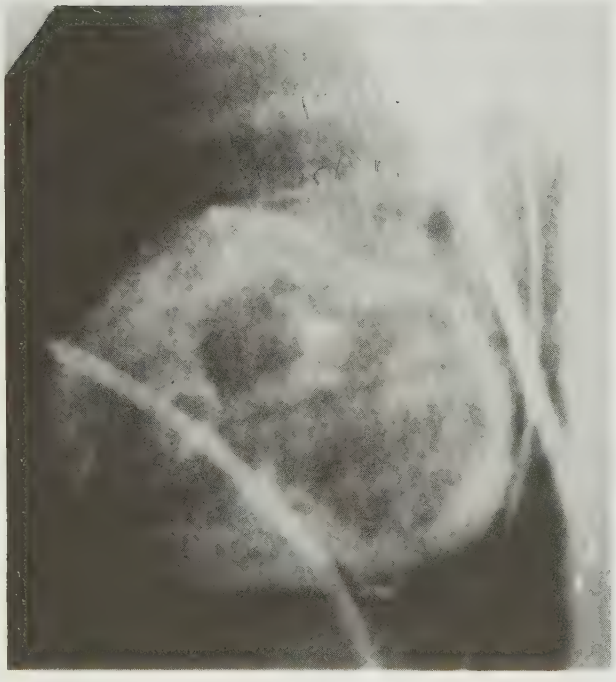

Fig. 65–7. Lateral view of a right ventricular angiogram in a patient with PA-IVS after the contrast material has almost cleared. The very small tricuspid orifice is well outlined, and accurate measurement is possible by comparing it to the 5F catheter.

main pulmonary artery. This distance can be adequately appreciated by opacification of both the main pulmonary artery and the right ventricle simultaneously with injection of contrast material in the descending aorta at the level of the ductus and in the right ventricle at the same time using two catheters as described by Freedom and colleagues.[63] The umbilical artery indwelling catheter can be used for the aortogram. An alternative method of ascertaining the distance is by labeling the tip of the outflow tract on the cine screen and noting its proximity to the pulmonary artery later in the injection as the aorta and pulmonary arteries opacify.

A left ventricular injection will show the size and function of the left ventricle and will eliminate the possibility of a ventricular septal defect. Good opacification of the aorta occurs if the catheter is well placed in the left ventricle, and the pulmonary arteries will opacify via the ductus arteriosus or other collateral circulation. A posteroanterior projection with cephalic angulation shows the anatomy and size of the branch pulmonary arteries, while the lateral projection reveals the presence or absence of a main pulmonary artery and shows its size. If a left ventricular injection is not possible with the venous catheter, then an aortogram should definitely be done either with the umbilical catheter or by introducing a retrograde catheter into the femoral artery. Left ventricular compliance and function measured at the time of the original catheterization are felt to be important to the eventual outcome of these infants.[64]

DIFFERENTIAL DIAGNOSIS

Other lesions to be considered in newborns with severe cyanosis include d-transpositon of the great arteries, tetralogy of Fallot with or without pulmonary atresia, severe pulmonary stenosis with intact ventricular septum, tricuspid atresia, and total anomalous pulmonary venous return with obstruction of pulmonary veins. Rarer defects include complex defects associated with asplenia or polysplenia syndromes and pulmonary atresia with endocardial cushion defect or pulmonary atresia with double-outlet right ventricle.

ASSOCIATED DEFECTS

PA-IVS usually occurs as a single lesion. However, it has been reported in L-transposition of the great arteries and ventricular inversion,[65,66] with Uhl's anomaly,[67,68] and with aortic valve stenosis.[40,43]

TREATMENT

Medical

Adequate treatment of PA-IVS begins in the neonatal period with the onset of symptoms. As soon as the diagnosis of heart disease with decreased pulmonary blood flow is made, access to the vascular system should be established and an infusion of prostaglandins started to re-establish pulmonary blood flow. This infusion should result in a pink baby with good peripheral perfusion and a normal acid-base balance. An arterial line should be established, most easily done in the umbilical artery, since the infant will need frequent determinations of arterial blood gases especially during and following surgery. Abnormalities of glucose, calcium, or other electrolytes should be corrected.

During cardiac catheterization, a balloon atrial septostomy should be performed. In older infants with an inadequate atrial communication, a transseptal puncture followed by blade septostomy or surgical septectomy might be required.

Surgical

Analysis of the anatomy delineated by the catheterization dictates the mode of surgical intervention required. The surgical treatment of PA-IVS has always been somewhat disappointing because of the high mortality rate from this defect, even when it has seemingly been well palliated. Generally, the goals of surgery have been to establish adequate pulmonary blood flow by either a systemic-to-pulmonary shunt or ductus infiltration with formalin[69] (now rarely done), to create a communication between the right ventricle and pulmonary artery, or a combination of these procedures. The order and timing of these interventions have varied over the years.

To best appreciate the current views on the surgical treatment of PA-IVS, we present a historical review of publications concerning the surgical approach to the defect. Of initial importance is the concept of the creation of systemic-to-pulmonary artery shunt advanced by Blalock and Taussig[70] in 1945 followed by another approach proposed by Potts and associates the following year.[71] Their suggestions remain an integral part of the treatment of PA-IVS to this day.

Direct surgical relief of stenotic pulmonary valves was reported almost simultaneously by Sellors[72] and Brock[73] in 1948. In the early 1950s, surgical relief of valvular pulmonic stenosis with intact ventricular septum became more common[74–76] and was performed in younger patients.[77] Until 1954, valvotomies were approached blindly through a transventricular puncture. In 1954, Swan and associates[78] described a transarterial approach in which the pulmonary valve was directly visualized and surgically opened. This technique was better suited for infants younger than 1 year.[79] In 1962, Benton and colleagues[80] reported attempts at pulmonary valvotomy in patients with PA-IVS with no survivors; and in 1967, Gerson and colleagues[49] reported dismal results of attempts at various types of operations on infants with PA-IVS.

Published series of the next decade were generally more encouraging.[46,48,57,60,81–90] It became evident that pulmonary valvotomy alone in infants with PA-IVS and tiny right ventricles did not suffice, and mortality remained high.[46,81] Systemic-to-pulmonary shunts combined with surgical atrial septectomies or balloon septostomies resulted in improved survival.[46,48,85,85] Greater success was achieved by staging surgery.[85] This was achieved by atrial septostomy at the time of catheterization followed by a systemic-to-pulmonary shunt and then pulmonary valvotomy several weeks or months later. In 1976, Trusler and associates[57] reported good success by balloon septostomy at catheterization followed by combined Potts anastomosis and pulmonary valvotomy at the same time. A more complete repair could then be accomplished later. It seemed that if blood flow through the right ventricle could be established, growth of the ventricular cavity might occur over time.[57,60,87,89,90] The use of prostaglandins in the late 1970s allowed infants to be in an improved state for the procedures, and overall survival increased.

The 1980s brought further refinement to the surgical treatment of PA-IVS. Patel and associates[36] analyzed factors that influenced the growth of the right ventricle postoperatively in patients with PA-IVS and focused attention to the size of the tricuspid valve as one of the limiting factors for allowing growth of the ventricle. The ability to establish right ventricular–pulmonary artery continuity was also felt to be an important criterion. The tripartite classification of the right ventricle of Bull and associates[25] elaborated on the factors necessary for the proper selection and timing of procedures.[27,40]

The use of Fontan-type anastomoses in hearts with very small tricuspid valves was reported in 1982.[27] Since then, a number of reports have been published describing improved results of surgery in PA-IVS.[40,91–103] Prior to a decision regarding complete correction, the use of balloon closure of the atrial communication during catheterization might help the physician to decide whether the right ventricle will accommodate the entire systemic venous flow.[91,104] In 1982, Puga and Uretzky described a method to establish continuity between the hypoplastic right ventricle and pulmonary artery without the use of extracorporeal circulation.[105] The presence of ventriculocoronary communications, which is associated with severe hypoplasia of the right ventricle and tricuspid valve, might be detrimental if the pressure in the ventricle is relieved.[32] Therefore a systemic-to-pulmonary shunt in the neonate followed later by the Fontan procedure might prove more successful.

A recent summary[103] suggests that the tricuspid valve should approach 70% of normal size for a good result from complete correction and that patients with smaller valves should have a modified Fontan procedure. In this series, patients undergoing eventual Fontan surgery had tricuspid valves that were an average of 44.4% of normal when measured angiographically. This approach summarizes current treatment of the defect.

PROGNOSIS AND FUTURE DEVELOPMENTS

Although some patients with PA-IVS have lived into early adulthood without surgery,[106–108] the prognosis of this lesion remains guarded, even with surgery. In 1978, Freedom and Keith[5] reported the experiences in Toronto and Buffalo with one third of cases dying by the second week of life and 50% dead by one month. In 1983, Lewis and colleagues[101] from Los Angeles reported a 33% mortality in 27 children with PA-IVS presenting between 1976 and 1982 who had undergone various surgical procedures. Surgical reports continue to improve.[100,102,103] However, since patient selection differs in the reported series, actual mortality rates are not comparable. The eventual outcome appears to depend on the presence or absence of sinusoid-coronary communications and the size of the tricuspid valve.

The use of newer imaging techniques such as nuclear magnetic resonance and positron emission tomography together with three-dimensional computer techniques of echocardiography will improve the noninvasive anatomical classification and measurements in patients with PA-IVS.

The use of autogenous skeletal muscle to enlarge a hypoplastic ventricle is a new concept that has appeal, since it has the potential of growth and would overcome the problems of tissue rejection of transplanted tissue. Attempts[109–111] to use autogenous skeletal muscle, usually the electrically stimulated diaphragm, have been unsuccessful because of muscle fatigue. Recently, there has been renewed interest in the use of skeletal muscle, especially with the development of fatigue resistance.[112–115] Macoviak and associates[116]

have successfully used latissimus dorsi muscle isolated with its neurovascular bundle and electrically stimulated to replace part of a right ventricle in dogs. This same preparation was also used[116] as a neoventricle to provide pulmonary blood flow where the right ventricle has been bypassed, as in the Fontan procedure. Thus the future treatment of PA-IVS should continue to improve as techniques are developed to replace or augment the right ventricle.

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CHAPTER 66

Tricuspid Atresia

David J Driscoll

Tricuspid atresia, the third most common form of cyanotic congenital heart disease, consists of complete agenesis of the tricuspid valve and absence of direct communication between the right atrium and right ventricle.[1,2] The prevalence of tricuspid atresia in clinical series of patients with congenital heart disease ranges from 0.3 to 3.7%.[2] The prevalence rate in autopsy series is 2.9%.[2] Tricuspid atresia occurs in approximately 1 in 15,000 live births.[2] There is no apparent sex predilection if all forms of tricuspid atresia are considered; however, that associated with transposed great arteries occurs more commonly in males.[2–4] Kreysig described tricuspid atresia in 1817, and Kühne described it in 1906.[5–7]

PATHOLOGY

Tricuspid atresia is divided into three types (Table 66–1) on the basis of the great artery relationship: I, normally related great arteries; II, D-transposed great arteries; and III, L-transposed great arteries. Approximately 70% of cases are type I, 23% are type II, and 7% are type III.

The three types are subclassified according to the presence (or absence) and size of the ventricular septal defect and the presence (or absence) of pulmonary atresia or stenosis.[8,9]

Weinberg[10] classified tricuspid atresia into five types on the basis of the relationship of the systemic venous atrium to the underdeveloped right ventricle: A) *muscular atresia* (the most common type), no evidence of tricuspid valve tissue and the floor of the systemic venous atrium is muscular; B) *membranous atresia,* a portion of the right atrial floor is formed by a translucent membrane; C) *valvar atresia*, the floor of the systemic venous atrium contains a tiny imperforate valvelike structure; D) *Ebstein's form,* valvular tissue in the floor of the systemic atrium is adherent to the right ventricular wall, forming an "atrialized portion" of the right ventricle; and E) rarely, *common atrioventricular canal,* a leaflet of the common atrioventricular valve completely seals the only entrance to the right ventricle. Some investigators would exclude Weinberg's types D and E from tricuspid atresia, classifying these as Ebstein's anomaly with an imperforate valve and an unbalanced or left ventricular dominant atrioventricular canal defect, respectively.

Table 66–1. Classifications of Tricuspid Atresia

		Relative Frequency, %	
Type	*Description*	*Clinical*	*Autopsy*
I	Normally related great arteries	70	69
I-A	No VSD*; pulmonary atresia		9
I-B	Restrictive VSD; pulmonary stenosis		51
I-C	Large VSD; no pulmonary stenosis		9
II	D-Transposition of great arteries	23	28
II-A	VSD; pulmonary atresia		2
II-B	VSD; pulmonary stenosis		8
II-C	VSD; no pulmonary stenosis		18
III	L-Transposition of great arteries	7	3

Adapted from Rosenthal, A., and Dick, M.: Tricuspid atresia. *In* Moss' heart disease in infants, children, and adolescents. 3rd ed. Edited by F.H. Adams and G.C. Emmanouilides. Baltimore, Williams & Wilkins, 1983, pp. 271–283.

*VSD, ventricular septal defect

In tricuspid atresia the right ventricle is hypoplastic and may be a slitlike space concealed in the right wall of the left ventricle, a moderate-sized chamber with or without rudimentary papillary muscles, or a small chamber comprising a smooth-walled conus portion and a trabecular portion; however there is no sinus portion of the right ventricle (Fig. 66–1).[11]

Four types of ventricular septal defects can be associated with tricuspid atresia: 1) perimembranous type, 2) malalignment type, 3) muscular type, and 4) atrioventricular canal type. The perimembranous ventricular septal defect is located inferior to the parietal band, and the septal and parietal bands are relatively preserved. The conal septal malalignment defect occurs in a position normally occupied by the parietal band between the anterosuperior and posteroinferior septal bands. Muscular ventricular septal defects may be single or multiple and are located in the inferior aspect of the ventricular septum. The atrioventricular canal type (located in the posterior aspect of the septum) is rare. The ventricular septal defect may be, or may become, restrictive, producing subpulmonary or subaortic stenosis, depending on whether the great arteries are normal or transposed.

The pulmonary stenosis associated with tricuspid atresia can be valvular, subvalvular and unrelated to the ventricular septal defect, or due to a restrictive ventricular septal defect in patients with normally related great arteries. Pulmonary stenosis is more frequently associated with tricuspid atresia and normally related great arteries than with transposed great arteries. Although Weinberg[12] indicated that pulmonary stenosis is valvular in two-thirds of the patients with tricuspid atresia, other investigators believe that obstruction at the level of the ventricular septal defect is more common.

An opening in the atrial septum is necessary to allow egress of blood from the right atrium. In 80% of cases, there is a patent foramen ovale or a secundum atrial septal defect. Rarely, an ostium primum type of atrial septal defect is present. The interatrial communication can be or can become restrictive.

Additional cardiovascular abnormalities occur in 18% of patients with tricuspid atresia and normally related great arteries and in 63% of patients with transposed great arteries.[1,12,13] Persistence of the left superior vena cava with drainage into the coronary sinus occurs in 12 to 15% of patients with tricuspid atresia,[14] compared to 0.5% in the general population[15] and 4% in patients with congenital heart disease.[16] In the presence of bilateral superior venae cavae, the right superior vena cava may be too small (i.e., carry insufficient systemic venous return) to allow a successful Glenn anastomosis between the right superior vena cava and the right pulmonary artery. If an innominate vein connects the right and left superior venae cavae, blood flow may preferentially flow from the right superior vena cava and the Glenn anastomosis to the persistent left superior vena cava, reducing the effectiveness of the Glenn procedure. Rarely, the persistent left superior vena cava communicates directly with the atrium, a situation that must be identified and managed appropriately if the Fontan operation is contemplated.

Juxtaposed atrial appendages occur in 10% of all cases of tricuspid atresia but may be found in as many as 40% of cases of tricuspid atresia associated with transposed great arteries.[3,17] The presence of juxtaposed atrial appendages may necessitate alteration in the operative technique in establishing a right atrium-to-pulmonary artery connection for a modified Fontan operation.

Additional cardiovascular abnormalities associated with tricuspid atresia include coarctation of the aorta (8%), patent ductus arteriosus (3%), and right aortic arch (3 to 8%).[1,10,13] Extracardiac anomalies occur in 20% of the cases.[17]

After penetrating the central fibrous body of the heart, the bundle of His is related to the left ventricular aspect of the septum. However, the left bundle branch originates early from the bundle of His and is unusually more posteriorly located and shorter in tricuspid atresia than in the normal heart.[1,18] Presumably, this anatomic malformation of the conduction system accounts for the abnormal frontal plane axis of the electrocardiogram in patients with tricuspid atresia. The atrioventricular node is located in the

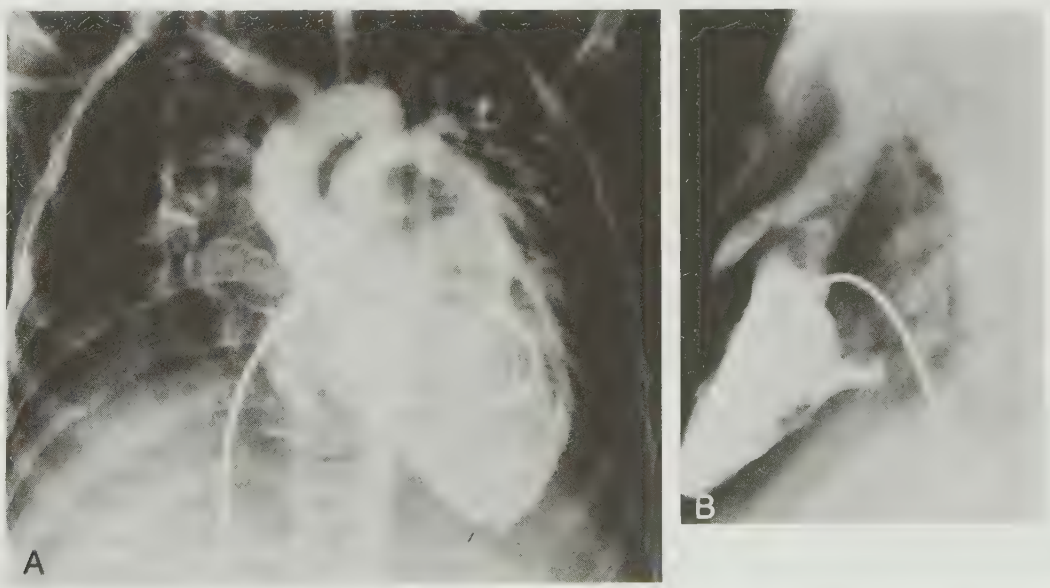

Fig. 66–1. A left ventriculogram in the anteroposterior and lateral projections in a patient with tricuspid atresia demonstrating a small right ventricle with absence of the inlet portion of the right ventricle. A restrictive ventriculoseptal defect is seen in the lateral projection.

region of the tendon of Todaro, and, unlike the abnormally located anterior atrioventricular node in some cases of univentricular heart, it is normally located posteriorly.

HEMODYNAMICS

Systemic venous blood returning to the right atrium can exit from the right atrium only through an interatrial communication (Fig. 66–2). If the interatrial communication is small, the right atrial pressure may be increased. However, with low cardiac output and a restrictive septal defect, a pressure difference between right and left atrium may be unimpressive. Because of the obligatory right-to-left shunt at atrial level, left atrial blood oxygen saturation is decreased but pulmonary venous blood saturation is normal.

In tricuspid atresia, the hemodynamics depend on the presence or absence of pulmonary atresia, the degree of pulmonary stenosis, the presence of normally related or transposed great arteries, and the presence or absence of subpulmonary or subaortic stenosis at the level of the ventricular septal defect. Because all systemic venous return (blood oxygen saturation low) and pulmonary venous return (blood oxygen saturation high) mix in the left atrium, the level of blood oxygen saturation reaching the left ventricle, and subsequently the aorta, depends on the relative volumes of pulmonary venous return and systemic venous return. Patients with tricuspid atresia and increased pulmonary blood flow (i.e., no pulmonary or subpulmonary stenosis) have a relatively larger volume of pulmonary venous return than systemic venous return and have relatively high systemic arterial blood oxygen saturation. In contrast, patients with relatively low pulmonary blood flow (due to pulmonary or subpulmonary stenosis or pulmonary atresia) may have marked systemic arterial hypoxemia. The volume of pulmonary blood flow and the clinical characteristics may change with time. Patients with pulmonary stenosis may be dependent on patency of the ductus arteriosus for pulmonary blood flow and, as the ductus closes, pulmonary blood flow may decrease significantly.

Fig. 66–2. A schematic diagram representing the course of blood flow in a heart with tricuspid atresia.

In general, pulmonary or subpulmonary (at the level of the ventricular septal defect) obstruction is present or occurs during the first year of life in most patients with tricuspid atresia and normally related great arteries. In contrast, most patients with tricuspid atresia and D-transposed great arteries (type II) have unobstructed pulmonary blood flow. Hence, patients in the former groups usually will have more marked hypoxemia than those with D-transposed great arteries, but those with D-transposed great arteries are more likely to have pulmonary edema and congestive heart failure and to develop pulmonary vascular obstructive disease. The ventricular septal defect associated with tricuspid atresia tends to become smaller with time. A restrictive ventricular septal defect associated with normally related great arteries produces progressive subpulmonary stenosis and increasing hypoxemia. A restrictive ventricular septal defect associated with transposed great arteries produces subaortic obstruction. When combined with pulmonary stenosis or the presence of a pulmonary artery band, significant left ventricular hypertension and hypertrophy occur. Severe left ventricular hypertrophy may affect the outcome of a Fontan operation adversely.

The major portion of the ventricular mass in tricuspid atresia is composed of left ventricle and functionally is a single ventricle. Because it receives all systemic and pulmonary venous return, the ventricle functions with a volume overload. This, in addition to long-standing hypoxemia, may contribute to ventricular fibrosis and decreased function that is manifested by increased left ventricular end-diastolic pressure and decreased ejection fraction. Decreased ventricular function may also result in mitral annular dilation and mitral insufficiency.

CLINICAL HISTORY

Because of the presence of cyanosis, congestive heart failure, or growth failure, tricuspid atresia usually is detected in infancy. At the Boston Children's Hospital, all but one patient with tricuspid atresia required hospitalization by 6 months of age.[1] In more than half of the patients, other symptoms of congenital heart disease developed in the first week of life, and 75% had cyanosis.[19]

The clinical presentation depends to a great degree on the amount of pulmonary blood flow. Cyanosis is the most prominent feature in patients whose pulmonary blood flow is limited by pulmonary atresia or pulmonary stenosis. Symptoms of pulmonary edema and congestive heart failure predominate in patients with unobstructed pulmonary blood flow; cyanosis also can be apparent. If pulmonary blood flow depends on the patency of the ductus arteriosus, the degree of cyanosis and arterial hypoxemia may increase dramatically if the ductus arteriosus closes. Indeed, if pulmonary atresia is present, closure of the ductus can produce

profound hypoxemia, acidosis, and death. Hypoxic spells have been reported in 16 to 45% of infants less than 6 months of age with tricuspid atresia, and death occurred in 4%.[1] Also, as pulmonary vascular resistance decreases and pulmonary blood flow increases in early infancy, the signs and symptoms of congestive heart failure and pulmonary edema can increase in patients who do not have pulmonary stenosis. Usually, however, the course in patients with normally related great arteries is one of aggressive cyanosis.

Growth failure is common in infants with tricuspid atresia. Dick[19] reported that 19% of such newborns were less than the fifth percentile for weight, suggesting intrauterine growth failure. Postnatal growth also was impaired: 58% of their patients were less than the fifth percentile for weight and 52% were less than the fifth percentile for height at the time of their last examination. Without surgical intervention, significant pulmonary vascular obstructive disease will occur in patients with unrestricted pulmonary blood flow (types I-C and II-C). Pulmonary vascular obstructive disease is much less common in patients with tricuspid atresia and normally related great arteries than in patients with transposed great arteries because the majority of patients with normally related great arteries have or develop either pulmonary or subpulmonary stenosis.

Bacterial endocarditis and brain abscess are relatively common complications of tricuspid atresia. Bacterial endocarditis occurs in 17 to 25% of patients with tricuspid atresia who have had a surgical systemic-to-pulmonary artery anastomosis. This represents one episode of endocarditis per 72 patient·years.[3,4] Brain abscess occurs in 1.3 to 5% of patients, representing one episode of brain abscess per 273 patient·years.[19,20] Brain abscess should be suspected in any patient with cyanotic congenital heart disease and headache, focal neurologic signs, or seizures. Neurologic complications also can result from cerebrovascular accidents secondary to polycythemia or to intravascular thrombosis or embolic phenomena.

Thoracolumbar scoliosis is common in patients with cyanotic congenital heart disease, and appropriate management is necessary to avoid significant pulmonary compromise as well as cosmetic disability.

PHYSICAL EXAMINATION

Inspection

Cyanosis is the most common clinical feature of tricuspid atresia, and the degree of cyanosis is dependent on the amount of pulmonary blood flow. In newborns with tricuspid atresia, pulmonary atresia, or stenosis, the amount of pulmonary blood flow is decreased, and cyanosis will worsen as the ductus arteriosus closes. Infants with tricuspid atresia and normally related great arteries may have excessive pulmonary blood flow and little cyanosis. As the ventricular septal defect becomes progressively more restrictive, causing subpulmonary stenosis and decreasing blood flow, signs and symptoms of congestive failure and pulmonary edema will lessen and the degree of cyanosis will increase. Because of cyanosis and polycythemia, digital clubbing is common after 3 months of age. Jugular venous pulsations are difficult to assess in infants. In children and adults with tricuspid atresia the jugular venous pulsations can be abnormal. A prominent a wave can occur if the interatrial communication is restrictive, and a prominent v wave may be found in the presence of mitral insufficiency with an unrestricted interatrial communication.

Palpation

The peripheral pulses and pulse volume may be normal, increased, or decreased. Patients with a patent ductus arteriosus, numerous or large aorticopulmonary collateral vessels, or a surgically created systemic-to-pulmonary artery anastomosis may have an increased pulse volume. A discrepancy between the upper and lower extremity pulse volumes is indicative of associated coarctation of the aorta. The pulse volume may be decreased in patients with transposed great arteries and a restrictive ventricular septal defect (subaortic stenosis). The peripheral arterial pulses should be normal in patients without a surgically created aorticopulmonary anastomosis with a closed ductus arteriosus, absence of aorticopulmonary collateral vessels, and no coarctation of the aorta. The peripheral pulses are unaffected by a Glenn anastomosis.

Tricuspid atresia is one form of cyanotic congenital heart disease that results in the left ventricular impulse being more prominent than the right ventricular impulse. Because the left ventricle is subjected to volume overload, the apical impulse is overactive and usually is displaced to or beyond the left midclavicular line. Closure of the aortic valve may be palpable at the upper left sternal border in patients with tricuspid atresia and transposed great arteries. A thrill may be felt at the left sternal border in patients with pulmonary stenosis or restrictive ventricular septal defect. The liver may be enlarged and pulsatile, especially if there is a restrictive interatrial communication or mitral insufficiency.

Auscultation

The first heart sound is single but may be of increased intensity. The second heart sound may be single or split normally with respiration. The intensity of the second heart sound usually is normal if the great arteries are normally related and the pulmonary artery pressure is normal. Because of the proximity of the aorta to the anterior chest wall when transposed great arteries are present (i.e., the aorta is anterior to the pulmonary artery), the second heart sound may be increased in intensity despite normal pulmonary artery pressure.

Cardiac murmurs are present in 80% of patients with tricuspid atresia.[13] A low-frequency holosystolic or, at times, crescendo-decrescendo murmur will be produced from blood flowing through the ventricular septal defect. A systolic midfrequency crescendo-decrescendo murmur is present in patients with pulmonary stenosis. Patients with pulmonary atresia and a systemic-to-pulmonary collateral blood supply, as well as patients who have had a surgical systemic arterial-to-pulmonary arterial anastomosis, have a continuous murmur. In contrast, murmurs are not produced by an unobstructed Glenn anastomosis (connection of superior vena cava to right pulmonary artery). A diastolic mitral murmur may be audible in patients who have excessive pulmonary blood flow. A murmur of mitral insufficiency may occur, but frequently other systolic murmurs obscure this murmur even if mitral insufficiency is present.

ELECTROCARDIOGRAM

The cardiac rhythm in tricuspid atresia usually is sinus with tall P waves suggesting atrial enlargement (Fig. 66–3). First-degree

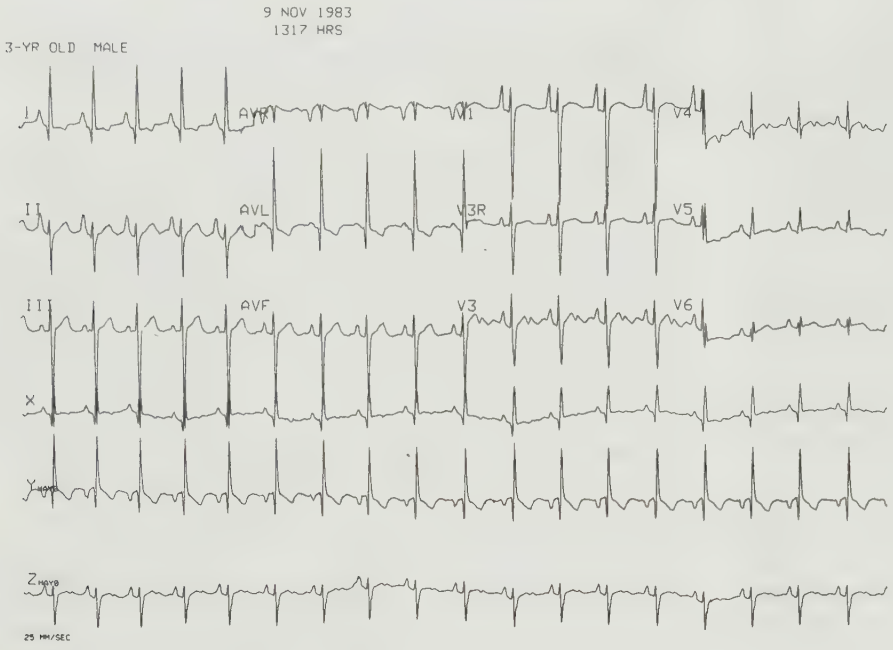

Fig. 66–3. An electrocardiogram from a patient with tricuspid atresia. The frontal plane QRS axis shows left axis deviation. The P waves are tall and peaked, suggesting right atrial enlargement. Anterior (right ventricular) forces are relatively diminished.

atrioventricular block occurs (15% of cases). This presumably is due to prolonged intra-arterial conduction because atrioventricular node function usually is normal.[1] Because of early origin of the left bundle branch from the common bundle, the frontal plane QRS axis usually is leftward or superior. Rarely, the frontal plane QRS axis is normal, which suggests the presence of transposed great arteries.[13,21] Right ventricular electrocardiographic forces are diminished and there is evidence of left ventricular hypertrophy. Frequently discordant QRS and T waves are seen. There is poor correlation between P-wave amplitude and interatrial communication size. There is poor correlation between the amplitude of the QRS and the ventricular septal defect size or ventricular wall thickness.[21]

The surface electrocardiographic tracing may suggest the presence of preexcitation (i.e., short PR interval and apparent delta wave) in 9% of patients with tricuspid atresia, but an atrioventricular bypass tract can be demonstrated less frequently (T. Zellers, personal communication).

CHEST RADIOGRAPH

The heart usually is enlarged. Heart size depends upon the amount of pulmonary blood flow and the presence or absence of mitral insufficiency. The right heart border frequently is prominent reflecting enlargement of the right atrium. The pulmonary vascular markings are increased when the pulmonary blood flow is excessive. In 80% of patients with tricuspid atresia, the pulmonary blood flow is diminished and the pulmonary vascular markings are decreased.[22] A right aortic arch occurs in 3 to 8% of cases.[1,13]

ECHOCARDIOGRAM

Echocardiography can provide the diagnosis of tricuspid atresia and delineation of anatomic details and associated abnormalities.[23] The basic anatomy, the size of the atrial septal defect, the size of the ventricular septal defect, ventricular function, great artery relationships, and valvular function can be ascertained by using M-mode, two-dimensional, and color-flow imaging echocardiography. Relatively accurate estimates of pressure gradients (pulmonary stenosis, subaortic stenosis) can be made with Doppler techniques. Associated abnormalities, such as coarctation of the aorta, persistent left superior vena cava, and juxtaposed atrial appendages,[24] can be detected.

CARDIAC CATHETERIZATION

The role of cardiac catheterization in determining anatomic and hemodynamic details in congenital heart disease has changed dramatically with the increasing sophistication of noninvasive imaging techniques (echocardiography, magnetic resonance imaging). If one has high-quality noninvasive diagnostic imaging techniques available, cardiac catheterization no longer is required to determine the presence of tricuspid atresia, great artery relationships, presence or absence of pulmonary stenosis, or the size of the interatrial communication. The role of cardiac catheterization depends to a large extent upon the patient's age.

In infants, the major use of cardiac catheterization is for determining the sources and reliability of pulmonary blood flow. With associated pulmonary atresia or severe pulmonary stenosis, patent ductus arteriosus may be the only source of sufficient pulmonary blood flow. Ventriculography or aortography, or both, may be necessary to document an alternate source of pulmonary blood flow, such as systemic-to-pulmonary artery collateral vessels. The administration of prostaglandin E_1 to maintain ductal patency has improved the safety of cardiac catheterization for babies with decreased pulmonary blood flow. Cardiac catheterization may be necessary in infants (2 to 6 months of age) for measurement of pulmonary artery pressure and resistance, as a guide to the need of pulmonary artery banding to prevent the development of pulmonary vascular obstructive disease. Some investigators recommend balloon atrial septostomy for all infants with tricuspid atresia. Others indicate that only a small subset of infants with tricuspid atresia have a restrictive interatrial communication, and septostomy should be done only in this subset of patients. If a systemic-to-pulmonary shunt is performed, it is

thought by some that the increased volume of blood returning to the left atrium may tend to close the valve of the foramen ovale. For this reason, some investigators perform balloon septostomy immediately before or after aorticopulmonary shunt. Occasionally, a previously unrestrictive interatrial communication becomes restrictive. In these cases the Park blade atrial septostomy technique can be used to enlarge the interatrial communication.[25]

In adolescents and adults, cardiac catheterization and angiography are used to define anatomic and hemodynamic details important in surgical management. If a Glenn anastomosis is contemplated, the presence of bilateral superior venae cavae must be excluded and the size and location of the single superior vena cava must be established. The presence of bilateral superior venae cavae will affect the function of the Glenn anastomosis adversely.

It is necessary to perform cardiac catheterization and angiography to obtain much of the following information that is important to have when a modified Fontan operation is being considered: 1) pulmonary artery size, distribution, and presence of pulmonary artery distortion from previous aorticopulmonary shunt, 2) pulmonary arteriolar resistance, 3) left ventricular function and end-diastolic pressure, 4) presence and severity of subaortic obstruction (especially in patients with transposed great arteries), 5) mitral valve competency, 6) presence and location of anomalous systemic or pulmonary venous drainage, and 7) presence of pulmonary arteriovenous fistula resulting from prior Glenn anastomosis.

CLINICAL MANAGEMENT

Infants

Three major considerations should guide the management of infants with tricuspid atresia: 1) manipulation of the amount of pulmonary blood flow, either to decrease hypoxemia and polycythemia by increasing pulmonary blood flow or to decrease symptoms of congestive heart failure by decreasing pulmonary blood flow, 2) preservation of myocardial function, pulmonary vascular integrity, and the pulmonary vascular bed to optimize conditions for future Fontan operation, and 3) reduction of risks of associated cardiovascular complications such as bacterial endocarditis and thromboembolism.

Most infants with tricuspid atresia have decreased pulmonary blood flow, marked cyanosis, and hypoxemia. With significant hypoxemia (systemic arterial oxygen tension less than 25 to 30 mm Hg), acidemia may occur and death ensue. These babies with severe hypoxemia should be treated promptly with an infusion of prostaglandin E_1 to maintain patency of the ductus arteriosus and thus improve pulmonary perfusion. Cardiac catheterization and angiography will be necessary to establish the sources of pulmonary blood flow and to plan for the appropriate type of surgical systemic-to-pulmonary artery anastomosis. A modified Blalock-Taussig shunt is the preferred systemic-to-pulmonary artery anastomosis for increasing pulmonary blood flow in infants with unacceptable levels of hypoxemia. This type of shunt is associated with the least amount of pulmonary artery distortion and the greatest degree of control of the amount of pulmonary blood flow. The Waterston-Cooley shunt often results in distortion of the right pulmonary artery and unequal perfusion to the two lungs (Fig. 66–4). A Potts shunt should be avoided. The Potts shunt has disadvantages similar to the those of the Waterston-Cooley anastomosis, and, in addition, is still very difficult to remove at the time of Fontan operation.

Unfortunately, it is not feasible to perform a Glenn anastomosis in infants. However, in older children with tricuspid atresia, a Glenn anastomosis is attractive because, unlike systemic-to-pulmonary artery shunts, it does not produce an increased volume of blood for the ventricle to manage. A disadvantage of the Glenn anastomosis is the associated development of arteriovenous fistulae in the lung.

Infants with transposed great arteries and unrestricted pulmonary blood flow have signs and symptoms of pulmonary edema and congestive heart failure. They benefit from treatment with digitalis and diuretics. In most infants with tricuspid atresia and normally related great arteries who have unrestricted pulmonary blood flow in the newborn period, progressive subpulmonary obstruction develops and by age 1 year they have had sufficient reduction of pulmonary blood flow to ameliorate the symptoms of congestive heart failure and pulmonary edema. Indeed, rarely does a patient with tricuspid atresia and normally related great arteries require pulmonary banding to relieve symptoms related to increased pulmonary blood flow. However, these patients may require pulmonary artery banding to preserve normal pulmonary arteriolar resistance if an eventual Fontan operation is contemplated.

Infants with tricuspid atresia and transposed great arteries frequently have unrestricted pulmonary blood flow and signs and symptoms of pulmonary edema and congestive heart failure. They will require a surgical procedure to decrease pulmonary blood flow. Unfortunately, pulmonary artery banding in these patients may be associated with accelerated narrowing of the ventricular septal defect and, because of the presence of transposed great arteries, significant subaortic obstruction.[26] A combination of subaortic obstruction and pulmonary artery obstruction by the pulmonary band results in marked ventricular hypertrophy and significantly increases the risk of mortality or complications at the time of eventual physiologic correction using the Fontan operation.[27] Patients who have tricuspid atresia and transposition of the great arteries and who have had a pulmonary artery band require careful ongoing surveillance to detect development of subaortic obstruction. That obstruction must be relieved when it becomes significant.

Intelligent application of palliative procedures to control the amount of pulmonary blood flow significantly improves survival of infants with tricuspid atresia. With standard palliative surgical treatment, 50% or more of these patients survive to age 15 years.[3] However, these patients still are at risk for complications resulting from intracardiac right-to-left shunt such as paradoxic emboli, brain abscess, polycythemia, and stroke. They also remain at risk for developing the complications of chronic ventricular volume overload such as progressive cardiac dilation, myocardial fibrosis, ventricular dysfunction, mitral valve regurgitation, and arrhythmias.

Children and Adolescents

Until Fontan and Baudet[28] developed the concept of ventricular exclusion, palliative procedures to control pulmonary blood flow were the mainstay of surgical therapy for patients with tricuspid atresia. Fontan and Baudet constructed a Glenn anastomosis to direct superior vena caval systemic venous return to the right lung,

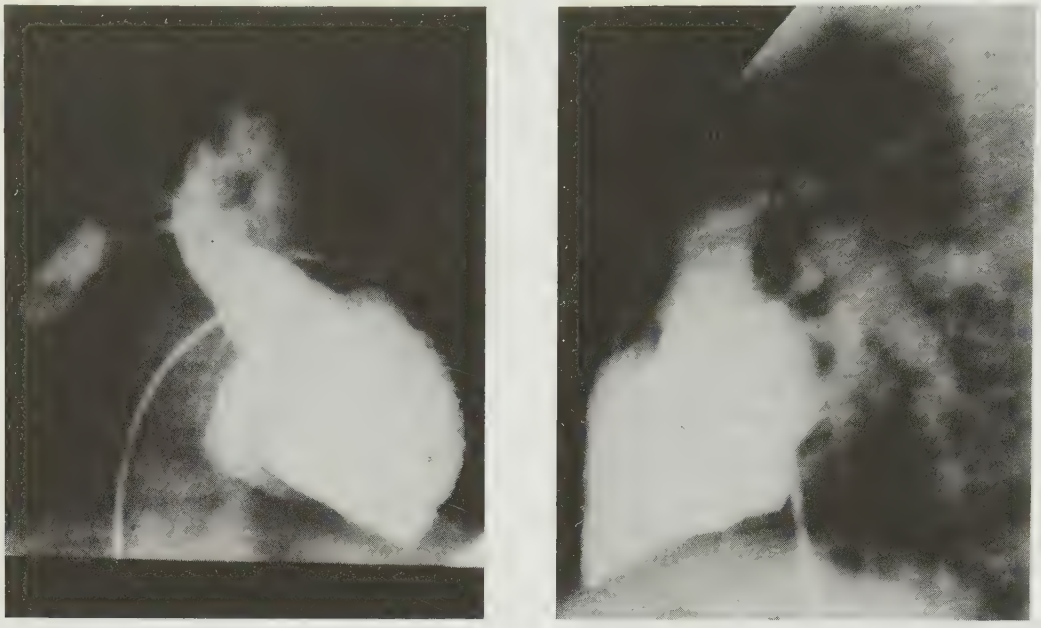

Fig. 66–4. Cineangiograms demonstrating distortion of the right pulmonary artery in association with a Waterston-Cooley shunt.

directed inferior vena caval systemic venous return to the pulmonary artery with a valve-containing conduit connecting the right atrium and pulmonary artery, inserted a valve into the inferior vena cava, closed the interatrial communication, and obliterated the connection between the pulmonary artery and the ventricle. Since the original description, the procedure has been modified considerably (Fig. 66–5), but the concept of directing systemic venous return directly to the pulmonary artery retains the eponym "modified Fontan procedure." It has become clear that use of prosthetic valves in the inferior vena cava and the right atrium-to-pulmonary artery connection is unnecessary. Prosthetic valves may be detrimental because of their tendency to malfunction and cause obstruction. Also, both superior vena caval and inferior vena caval systemic venous return can be directed from the right atrium to the pulmonary artery without utilizing a Glenn anastomosis. If there is a right ventricular remnant of reasonable size and a normal pulmonary valve, directing systemic venous return to the hypoplastic right ventricle with closure of the ventricular septal defect is advocated by some investigators rather than directing blood flow from right atrium to the pulmonary artery. Lee et al.[29] reviewed a series of patients with this type of connection and found no difference in operative survival or longterm results compared with those patients who had a right atrial-to-pulmonary artery connection.

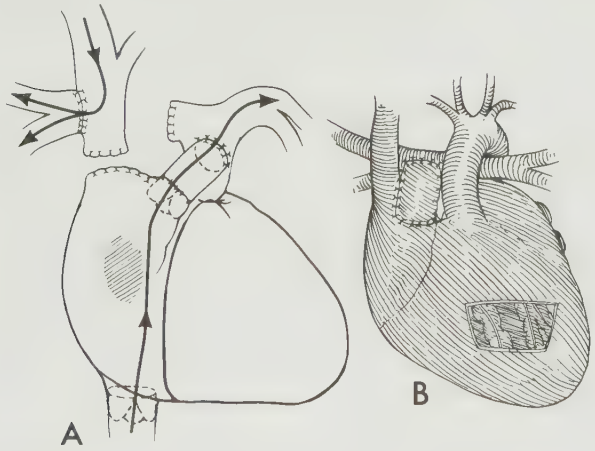

Fig. 66–5. (A) A diagram of the original procedure described by Fontan with prosthetic valves in the inferior vena cava and the connection between the right atrium and the main pulmonary artery. The superior vena cava is anastomosed to the right pulmonary artery. (B) The modified Fontan procedure, without prosthetic valves, and connection of the right atrium to a confluent pulmonary artery system.

Choussat and associates[30] developed ten guidelines for relatively low-risk operation (Table 66–2). It must be recognized that these are guidelines. Absence of one or more of these criteria does not eliminate the possibility of a modified Fontan operation. For example, Humes and associates[31] reported an operative mortality of 8% in 59 patients over age 17, a mortality not different from that of other age groups in his series. Also, in properly selected cases, the operation can be done at ages less than 4 years. Alboliras and

Table 66–2. Criteria of Choussat and Fontan for Low-Risk Operation

1.	Age at operation, 4 to 15 years
2.	Sinus rhythm
3.	Normal systemic venous return
4.	Normal right atrial volume
5.	Mean pulmonary artery pressure $\leq$15 mm Hg
6.	Pulmonary arteriolar resistance $<$4 units·m^2
7.	Pulmonary artery/aorta diameter ratio $>$0.75
8.	Left ventricular ejection fraction $\geq$0.60
9.	Competent mitral valve
10.	Absence of pulmonary artery distortion

Adapted from Choussat, A., et al.: Selection criteria for Fontan's procedure. *In* Pediatric Cardiology 1977. Edited by R.H. Anderson and E.A. Shinebourne. Edinburgh, Churchill Livingstone, 1978, pp. 559–566.

associates[32] reported an operative mortality of 25% for 12 patients who were not in sinus rhythm prior to operation. In addition, all 12 of these patients failed to fulfill 2 to 7 of the remaining 9 criteria of Choussat and associates.

Abnormal systemic and pulmonary venous connections can pose a challenge to the surgeon. With innovative intra-atrial baffle and conduit techniques to redirect blood flow to the pulmonary arteries, however, the Fontan operation can be performed successfully in spite of anomalies of venous connection. For example, a persistent left superior vena cava entering the dome of the left atrium can be anastomosed to the left pulmonary artery and the communication with the atrium obliterated. Systemic venous return of the right superior vena cava and inferior vena cava can be directed to the main pulmonary artery and right pulmonary artery, respectively in the usual fashion. The level of pulmonary arteriolar resistance is perhaps the most important criterion. It is unwise to recommend a modified Fontan operation if the pulmonary arteriolar resistance is above 4 units·m^2. On the other hand, increased pulmonary artery pressure is not a contraindication *if* the pulmonary resistance is less than 4 units·m^2. Mitral regurgitation can be managed with mitral valve annuloplasty or replacement. Kinking of pulmonary arteries from prior shunt procedures sometimes can be repaired to allow a successful modified Fontan operation. Patients with a longstanding Glenn anastomosis and acquired pulmonary arteriovenous fistulae present a unique problem as candidates for the Fontan operation. Because of the arteriovenous fistulae, they will remain hypoxemic (the degree of persistent hypoxemia depends upon the magnitude of the right-to-left shunt through the fistulae) after the Fontan operation. Attempts to eliminate the hypoxemia by repositioning the atrial septum to allow the right lower pulmonary vein to enter the right atrium (instead of the left) have been unsuccessful and should not be done. This technique is unsuccessful because the pulmonary artery pressure and the right lower pulmonary vein pressure become equal. Segmental pulmonary infarction occurs because of poor pulmonary blood flow.

Although the criteria of Choussat and Fontan are guidelines to low-risk Fontan operation and the operation can be done in the absence of some of these criteria, operative mortality and perhaps morbidity increase as more and more of these criteria are violated.

Postrepair right atrial pressure is a useful predictor of survival after the modified Fontan operation. In general, a postrepair mean right atrial pressure greater than 20 mm Hg portends a poor outcome. Kirklin, et al.[33] reported risk of death less than 12.5% if the mean right atrial pressure postrepair was less than 14 mm Hg but 43% if it was 19 mm Hg. Postrepair right atrial pressure reflects the adequacy of the right atrial-pulmonary artery anastomosis, pulmonary artery size, pulmonary arteriolar resistance, left atrial pressure, and left ventricular end-diastolic pressure. If one assumes a minimum 8 mm Hg transpulmonary pressure gradient postoperatively, a rough prediction of postoperative mean right atrial pressure can be made based upon preoperative assessment of left ventricular function, pulmonary artery size, and pulmonary arteriolar resistance.

Presumably the volume of the functional single ventricle should decrease after the modified Fontan operation and preliminary data suggest that this is so. Sanders, et al.[34] measured left ventricular ejection fraction before and after operation in 11 patients with tricuspid atresia who had a modified Fontan operation. Left ventricular ejection fraction remained normal postoperatively in 10 of these patients. In one case left ventricular ejection fraction was reduced preoperatively and remained reduced postoperatively.

Humes and associates[35] reviewed the results of the modified Fontan operation for patients with tricuspid atresia at the Mayo Clinic. Through June 1985, 134 patients with tricuspid atresia had a modified Fontan operation with an operative mortality of 10%. In addition, there were 11 late deaths. One-year survival was 85% and 5-year survival was 78%. Most of the survivors were doing well. Most of the patients reviewed by Humes failed to fulfill all of the criteria for low-risk operation. Operative mortality was less than 5% for patients fulfilling all, or all but one, of the criteria. Because the Fontan operation eliminates cyanosis and polycythemia and because the left ventricular volume overload is relieved, theoretically the operation should prolong life. Although there are early indications that it does prolong survival,[36] further longterm followup studies are necessary before this can be concluded firmly.

Most patients feel better after the Fontan operation, and exercise tolerance increases. Driscoll and associates[37] measured exercise tolerance in 33 patients with tricuspid atresia before Fontan operation and in 16 patients after operation. Maximal oxygen uptake increased from 39% of predicted preoperatively to 50% of predicted postoperatively. Systemic arterial blood oxygen saturation increased from 83 to 93% at rest and from 57 to 91% at peak exercise.

The modified Fontan operation can be performed with a low operative mortality, particularly in patients with tricuspid atresia who fulfill most of the Choussat and Fontan criteria for low-risk operation. Quality of life and exercise tolerance improve after operation. Preliminary data suggest that the operation prolongs life.[36] However, some patients continue to have problems postoperatively. These difficulties include fluid retention with ascites and peripheral edema, protein-losing enteropathy, and rarely, liver fibrosis.[38] Recurrence of an interatrial communication, dysfunction of a valve prosthesis, or spontaneous closure of a ventricular septal defect in patients with transposed great arteries may necessitate reoperation. Although some patients have persistent postoperative problems, in most circumstances the Fontan operation probably represents an improvement over the natural history of this malformation.

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CHAPTER 67

Truncus Arteriosus

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Robert J Sommerville

Persistent truncus arteriosus may be defined as a single great artery arising from the base of the heart giving origin to the coronary, pulmonary, and systemic arteries.[1,2] The earliest known descriptions of this defect were by Wilson in 1798,[3] and Buchanan in 1864.[4] The incidence of truncus arteriosus is rare, occurring in approximately 2% of patients with congenital heart defects.[5] There is no apparent gender predilection. Without treatment, truncus arteriosus is usually fatal, with the mean age of death at 2.5 months[6] and 80% of affected children dying by 1 year of age.[7]

EMBRYOLOGY

There are two embryologic theories on the development of truncus arteriosus. Classically, it is thought that the normal differentiation of the truncus into aorta and pulmonary artery is created by two ridges that appear in the conotruncal segment of the 4 to 5 mm (or 4 to 5 week) embryo. A spiral dextrodorsal ridge distally becomes continuous with a spiral sinistroventral ridge proximally. These two ridges grow toward the midline and become fused to form the conotruncal septum, which divides the truncus into the aorta and pulmonary artery with a 180° rotation.[8]

The semilunar valve site is marked by thickenings in the conotruncal ridge at the conotruncal junction. The right extension of the interventricular septum eventually coalesces with the conal portion of the conotruncal septum, thus separating the right and left ventricular outflow tracts.

The alternative theory was proposed by Van Praagh and Van Praagh. In their hypothesis, the 180° twisting of the great arteries about one another arises from the looping of the primitive ventricles to the right and subsequent differential conal growth forces the rotation of the aortic and pulmonary valves about a fixed point of the fourth and sixth arches. Van Praagh and Van Praagh have suggested that tetralogy and persistent truncus arteriosus may in fact be "first cousins"[6]; that is, persistent truncus arteriosus represents a form of tetralogy having pulmonary and infundibular atresia combined with failure of truncal separation.

ANATOMY

In 1949, Collett and Edwards proposed a classification based on embryologic theory and on their observations of 116 cases of persistent truncus arteriosus.[1] These authors classified (persistent) truncus arteriosus into 4 major types, based on the embryonic stage at which the development of the pulmonary arteries from the sixth aortic arches was arrested:

- Type 1—a single pulmonary trunk and ascending aorta arise from the truncus arteriosus.
- Type 2—the right and left pulmonary arteries arise close together from the dorsal wall of the truncus arteriosus.
- Type 3—one or both pulmonary arteries arise independently from either side of the truncus arteriosus.
- Type 4—no pulmonary arteries originate from the truncus and there is apparent absence of the sixth aortic arches. Pulmonary artery circulation is provided solely by bronchial arteries.

According to this classification, type 4 signifies arrested development at the earliest stage of the sixth aortic arches, since there is no development of the pulmonary arteries present. Types 3 and 2 represent arrested development at less primitive stages. Type 1

indicates arrested development at a much later stage with a portion of the common pulmonary trunk present (Fig. 67–1).

In 1965, Van Praagh proposed a new classification for truncus arteriosus. This classification is more complete and accurate than the classical one of Collett and Edwards (Fig. 67–1). Van Praagh classified two basic types—type A, with a VSD, and type B, without a VSD (rare). Both types are subdivided in terms of the great arteries: type 1—the aorticopulmonary septum is partially formed resulting in a partially separate main pulmonary artery; type 2—the aorticopulmonary septum is entirely absent, hence no discrete main pulmonary artery, with both pulmonary artery branches arising directly from the common trunk; type 3—absence of one pulmonary artery branch (either), this lung being supplied by collateral vessels; and type 4—the aortic isthmus displays hypoplasia, coarctation, atresia or absence, associated with a large patent ductus arteriosus. The vast majority of truncal cases have ventricular septal defect and belong to group A of Van Praagh. Group B recognizes the existence of persistent truncus without a ventricular septal defect.[9] Most authors, including Edwards,[10] agree that the type 4 Collett and Edwards classification does not represent a persistent truncus arteriosus, but rather an extreme form of tetralogy with main pulmonary artery atresia and commonly described today as pseudotruncus. In pseudotruncus the aortic pulmonary trunk is represented by a hard-to-find fibrous strand often identified only microscopically. Hemitruncus is not a true variant of truncus arteriosus, but a distinct anomaly in which conal-truncal division is complete. There is a pulmonary valve and a main pulmonary artery present, which gives rise to only one pulmonary artery branch. The pulmonary artery branch to the opposite lung arises directly from the ascending aorta.

Persistence of the truncus arteriosus almost always occurs in the presence of a ventricular septal defect. The truncal root straddles the ventricular septal defect equally in approximately 60% of cases with 20% each of the remaining cases having either a dominant right or left ventricular override.[11,12]

The truncal valve leaflets are usually abnormal and frequently appear thick, fleshy, soft, and polypoid. The number of leaflets varies. Approximately 65% have tricuspid valves; quadricuspid valves are present in 23% and bicuspid valves in approximately 9%. In 2% of cases, there may be five or more valve leaflets.[2,12] The truncal valve usually has fibrous continuity with the mitral valve and approximately 4 to 10% of cases may have a fibrous continuity with the tricuspid valve.[2,11] Truncal valve regurgitation is present in approximately 50% of patients, with half of these being moderate to severe.[13] Truncal valve stenosis may be seen in about one-third of patients, with a gradient ranging from 10 mm Hg to 60 mm Hg.[5]

Associated Abnormalities

The aortic arch is right-sided in about one-third of cases.[5] Persistent left superior vena cava is found in approximately 12% of cases. Partial anomalous pulmonary venous return is unusual, occurring approximately 1% of the time.[2,6] Abnormal origin of the coronary arteries is frequent.[12,14] A single coronary artery occurs

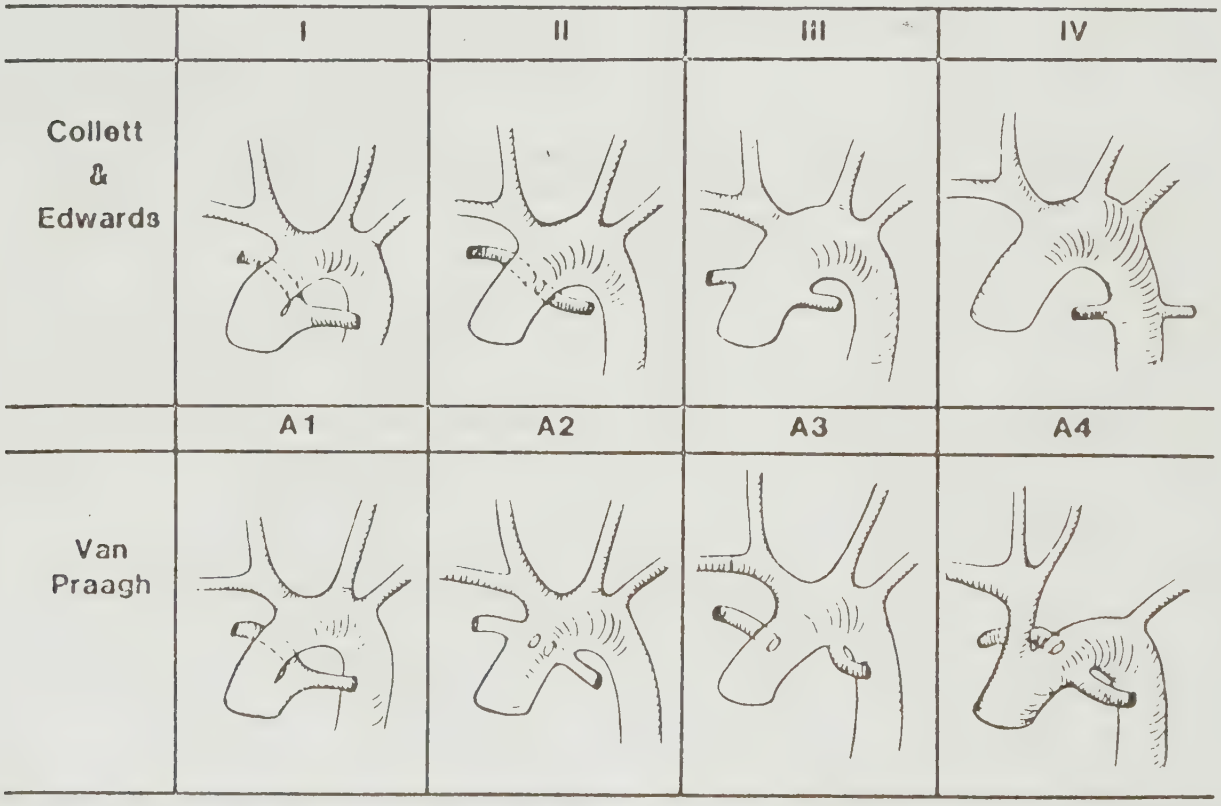

Fig. 67–1. Types of truncus arteriosus. The top row is modified from Collett and Edwards[1] and is still commonly referred to today. The bottom row is from Van Praagh and Van Praagh.[6]

in 13% of cases with truncus arteriosus. The coronary arteries may be separate, but near each other, arising from the same coronary sinus (10%). The left coronary artery tends to arise from a more posterior level than it does normally from the aorta. Anomalies of the posterior descending coronary artery branches are also common. The anatomy of the coronary arteries is of significance at the time of the surgical repair.

Tricuspid atresia and complete endocardial cushion defects have been reported with truncus arteriosus, as well as single ventricle.[15,16] Only one case of truncus arteriosus with intact ventricular septum has been reported.[9]

In approximately 12% of interrupted aortic anomalies, there is an associated truncus arteriosus.[17,18] Crisscross pulmonary arteries (a rare condition where the left pulmonary artery originates to the right of the origin of the right pulmonary artery, thus causing the pulmonary arteries to crisscross as they course to the respective lungs) is most frequently associated with truncus arteriosus and interrupted aortic arch.

Noncardiac anomalies are present in approximately 20% of cases.[6] DiGeorge's syndrome is one of the more common associated anomalies. Conversely, in those patients having DiGeorge's syndrome, which may be an autosomal dominant inheritance, approximately 26% have truncus arteriosus.[19,20] In those with DiGeorge's syndrome with interrupted arch, 33% have truncus arteriosus.[21]

PATHOPHYSIOLOGY

In truncus arteriosus there is obligatory mixing of the systemic venous and pulmonary venous blood at the level of the VSD and the base of the truncus. However, due to preferential streaming flow patterns the pulmonary artery saturation is often 10% lower than the systemic arterial saturation and truncus is not a total mixing lesion. The resultant systemic arterial saturation depends on the total volume of pulmonary blood flow, which varies inversely with the pulmonary arteriolar resistance. In the young infant, the pulmonary blood flow is often high because of the systemic pressure perfusing the pulmonary arteries with a relatively low resistance. This increased pulmonary vascular volume overloads the left heart and therefore symptoms of congestive heart failure are common at a very young age. At this stage of high pulmonary blood flow, there is minimal or no cyanosis. Progressive pulmonary vascular resistance may develop at an accelerated rate in truncus, which may result in irreversible vascular disease rendering the infant inoperable at a young age. Paradoxically, symptomatic improvement of CHF with reduced pulmonary blood flow results from increasing pulmonary resistance.

CLINICAL FEATURES

Patients with truncus arteriosus usually present with severe congestive heart failure during the first few months of life. Cyanosis is usually not clinically visible.[22] The severity of congestive heart failure not only is dependent on pulmonary blood flow volume, but it also may be aggravated by truncal valve regurgitation.

Tachypnea, decreased feeding, and irritability may be the first clinical symptoms. Although the symptoms usually occur within the first few days of life, they may be delayed up to several weeks, secondary to the delay in the decrease in pulmonary vascular resistance. Clinically, an infant with truncus arteriosus will present similarly to a patient with ventricular septal defect and ductus arteriosus or one with an aortopulmonary artery window and ventricular septal defect. Frequently, a systolic murmur is heard at the left sternal border; this murmur is usually holosystolic. This is accompanied by an ejection click and followed by a single second heart sound. Occasionally, an early diastolic murmur may be present from truncal valve regurgitation, or a continuous murmur may be present, if there is a pressure gradient from the truncal root to the branching of the pulmonary arteries or artery. Palpable peripheral pulses may become collapsing and sharp in contour secondary to the pulmonary artery run-off.

The electrocardiogram usually shows biventricular hypertrophy. Isolated right or left ventricular hypertrophy is less common.

The chest roentgenogram demonstrates cardiomegaly after the first day or two of life. The heart size continues to increase, as pulmonary overcirculation occurs with regression of fetal pulmonary vascular resistance. The left atrium becomes enlarged to accommodate the increased pulmonary venous return. As congestive heart failure progresses, the large pulmonary vessels become indistinct and obscured by pulmonary edema. The position of the aortic arch should always be identified. The finding of a right aortic arch with increased pulmonary vascular markings gives an extremely high probability of truncus arteriosus. If there is atresia of one of the pulmonary arteries, i.e., type A 3, then there will be asymmetry of the pulmonary vascularity, which may be associated with hypoplasia of the lung and hemithorax on the same side as the aortic arch.[22]

ECHOCARDIOGRAPHIC AND DOPPLER FEATURES

The echocardiogram evaluation usually is the first noninvasive test that can corroborate the clinical suspicion of truncus arteriosus. The long-axis parasternal view demonstrates a single great artery having a semilunar valve in continuity with the mitral valve. The truncal valve usually overrides the ventricular septum. The left atrium, in the absence of an atrial septal defect, is typically enlarged reflecting the increased pulmonary blood flow. With slight clockwise rotation of the transducer from the long axis, the origin of the left pulmonary artery is usually seen. With further rotation of the transducer into the parasternal short-axis view, both pulmonary arteries can be seen arising from the trunk. Visualization of both pulmonary arteries may be improved by sliding the transducer up one interspace.[23] In the subcostal four-chamber view, a dilated left ventricle and left atrium are again noted. In the standard subcostal long-axis view, the left ventricle and the truncus appear to originate from the left ventricle alone (Fig. 67–2). When the transducer is rotated slightly clockwise, the ventricular septum appears directed toward the truncal valve. The truncal root appears large and overrides the crest of the ventricualr septum. The left pulmonary artery can be seen originating from the posterior part of the trunk. The left atrial appendage is in close proximity to the left pulmonary artery and trunk. With counterclockwise rotation of the transducer, following the trunk toward the patient's right, both pulmonary arteries can then be seen. From the suprasternal view, the right pulmonary artery is seen in the long axis with the aorta in the short axis. In the long-axis view of the aorta, the origin of the left pulmonary artery can usually be seen above the valve. Again, the "sine qua non" of persistent truncus arteriosus

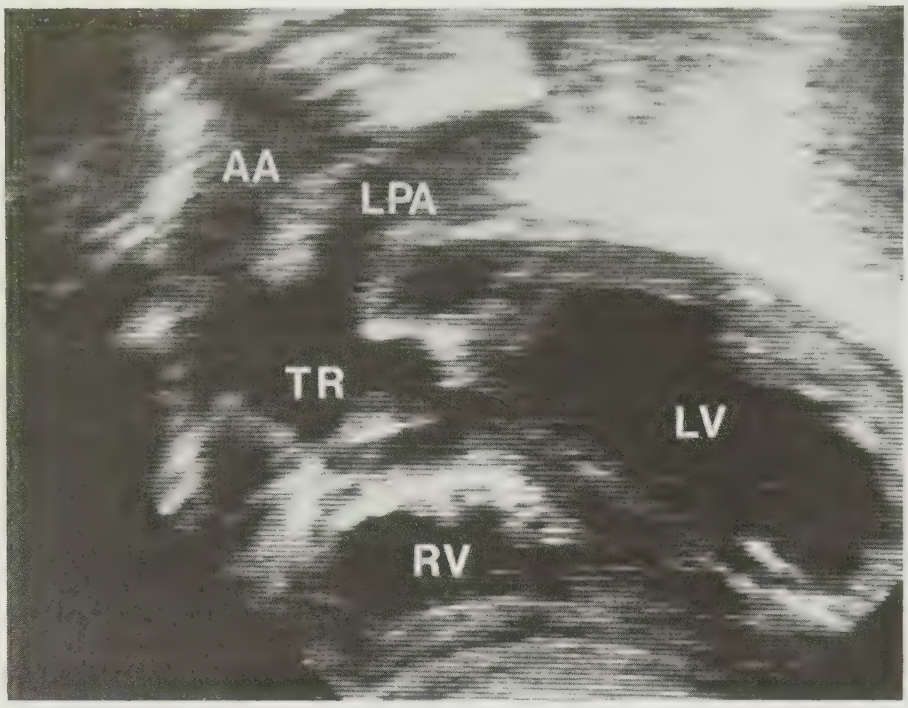

Fig. 67–2. Two-dimensional echocardiogram obtained from subcostal projection. The truncal root (TR) is located above the left ventricle (LV) and the right ventricle (RV). Consistent with the diagnosis of truncus arteriosus, the left pulmonary artery (LPA) is seen arising from the truncal root. (AA = aortic arch).

is the demonstration of the pulmonary arteries originating from a common trunk and semilunar valve. Doppler evaluation can accurately demonstrate the competency of the truncal valve. Further, color Doppler evaluation can better demonstrate the flow pattern across the truncal valve and competency of the valve. With parasternal, subcostal, and suprasternal views, differentiation of truncus arteriosus from a simple ventricular septal defect can be done with a high degree of accuracy.[23–26] However, problems may arise with differentiating truncus arteriosus from pulmonary atresia with ventricular septal defect.[24]

CARDIAC CATHETERIZATION AND ANGIOGRAPHIC FEATURES

Cardiac catheterization and angiography have long been the most definitive evaluation of the anatomical detail and physiologic variables in truncus arteriosus. Pressures in both ventricles are systemic and pressure in the left atrium is frequently elevated due to the increased pulmonary venous return. Although one would predict that in the common trunk there would be complete mixing, with the distal pulmonary artery and aortic arch having the same oxygen saturation, in practice this usually does not occur. Frequently, the pulmonary arterial saturation may be as much as 10% less than the aortic. This is due to streamlining of blood from the right ventricle into the pulmonary trunk. Further, there may be a drop in pressure in the more distal pulmonary arteries compared to the aortic arch. Evaluation of pulmonary arterial resistance was extremely important in the past when patients were over 2 years of age prior to surgical repair. Surgery was considered not feasible if the pulmonary arteriolar resistance was greater than 8 units M^2.[27] However, the present policy of doing corrective surgery by 6 months of age should prevent the steady progression of pulmonary arteriolar resistance to the point of pulmonary vascular disease.[28–30] Patients with truncus arteriosus and single pulmonary artery still remain at a large risk for pulmonary vascular obstructive disease postoperatively.[31,32]

Truncal angiography is imperative and we prefer to use the AP and lateral views for this. The ventriculograms are probably best done in the long axial oblique and elongated right anterior oblique views. Truncal angiography can usually be done with the catheter prograde across the truncal valve (Fig. 67–3), but on rare occasions may require retrograde study. From the selective truncal angiograms, an assessment of the valve can be made. The well-

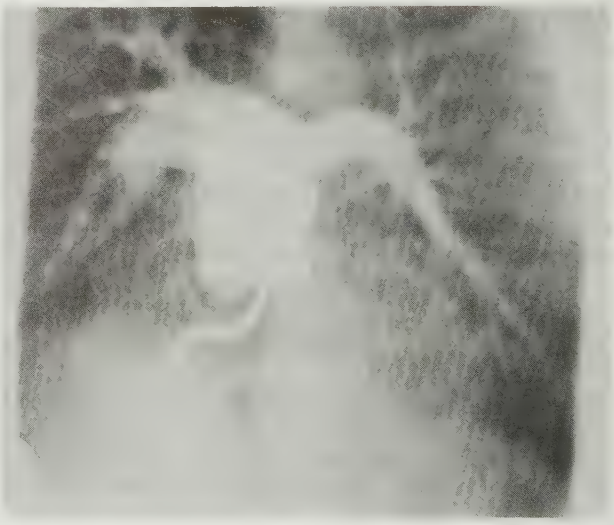

Fig. 67–3. Prograde truncal angiogram in the frontal view demonstrating truncal valve in diastole and distally the separation of the ascending aorta from the pulmonary arteries. (Angiogram courtesy of Dr. L.M. Bargeron, University of Alabama.)

formed tricuspid truncal valve can be identified using the AP and lateral views. The cusps are best seen in diastole. When the valve is bicuspid, the appearance of two valve structures is present. Dysplastic leaflets have irregular borders with poorly defined cusps. Many of these dysplastic valves will be quadricuspid. The variability of the coronary arteries can also be identified from this injection. The aortopulmonary septum with well-defined main pulmonary artery can also be visualized in this view. Usually the ventriculogram in the elongated right anterior oblique demonstrates the aortopulmonary septum well, but occasionally a truncal angiogram in the elongated right anterior oblique view may be needed to enhance the presence of an aortopulmonary septum.[11] If the aorta is noted to be significantly smaller than the pulmonary artery portion of the truncus, then an interrupted aortic arch should be expected.[33] The aortic arch is frequently right-sided and there may be a persistence of the ductus arteriosus. Anomalous subclavian artery is not unusual. Both peripheral pulmonary artery stenosis and origin of one of the pulmonary arteries from a ductus arteriosus with discontinuity of the pulmonary arteries also are not rare.[11]

The ventriculograms, perferably done from both ventricles, in both the long-axis and elongated right anterior oblique views, can delineate the anatomy and physiology of the truncus arteriosus. The long-axis view (Fig. 67–4) delineates the ventricular septal defect directly beneath the truncal valve area where the infundibular septum should be located. The left ventricular outflow tract is formed by the anterior leaflet of the mitral valve posteriorly and by the trabecular septum anteriorly. The right ventricular connection to the truncus arteriosus is bounded posteriorly by the septal structure and anteriorly by the ventriculoinfundibular fold. The elongated right anterior oblique view (Fig. 67–5) may demonstrate the right ventricular outflow to the truncus and also delineate the aortopulmonary septum of the truncus.[11] Frequently, the right ventriculogram will preferentially fill the pulmonary artery circulation. Due to the large volume of blood secondary to the mixing that occurs in truncus arteriosus, angiograms in the infant require large volumes of contrast (2 mL/kg), in order to delineate the necessary structures and mixing. Therefore, in our institution, we tend to use nonionic contrast for these studies.

Other forms of imaging truncus arteriosus may become more prevalent in the future. Magnetic resonance can accurately delineate the vessels and chambers in truncus arteriosus without the use of contrast material. Further, there is no exposure to ionizing radiation. In the future, it is possible that ultrafast computed tomography may be an imaging technique that can be used in truncus arteriosus. At the present time, magnetic resonance imaging and computed tomography are not routinely done in the work-up of truncus arteriosus.[34]

TREATMENT

The ultimate treatment for truncus arteriosus is surgical. However, the initial treatment is medical and should be aimed at cardiac decongestive therapy. In the neonate, diagnosis of classic truncus arteriosus is sufficient criteria for instigating cardiac decongestive therapy even without the signs or symptoms of congestive heart failure. As the pulmonary vascular resistance decreases, the congestive heart failure will assuredly occur. Congestive heart failure treatment consists of use of digitalis and aggressive diuretic therapy.

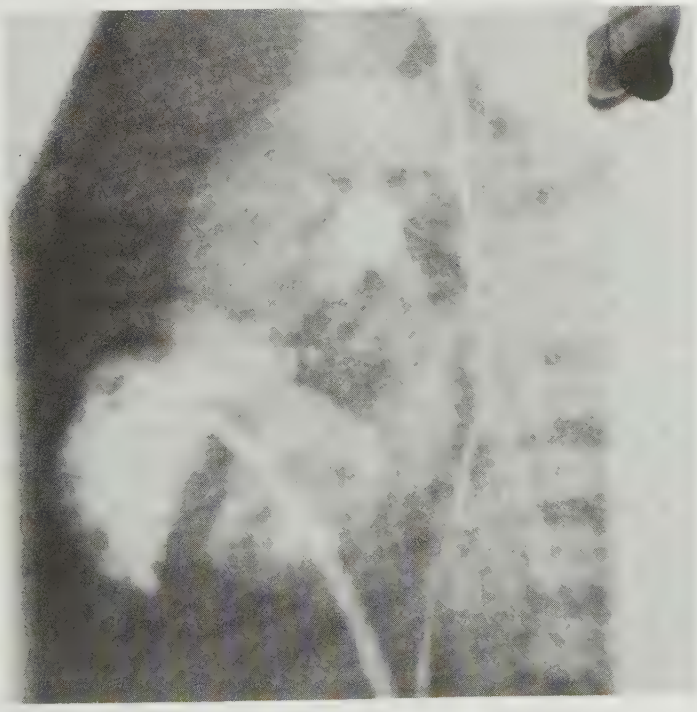

Fig. 67–4. Right ventriculogram in the long-axial view demonstrating ventricular septal defect immediately beneath the truncal valve. (Angiogram courtesy of Dr. L.M. Bargeron, University of Alabama.)

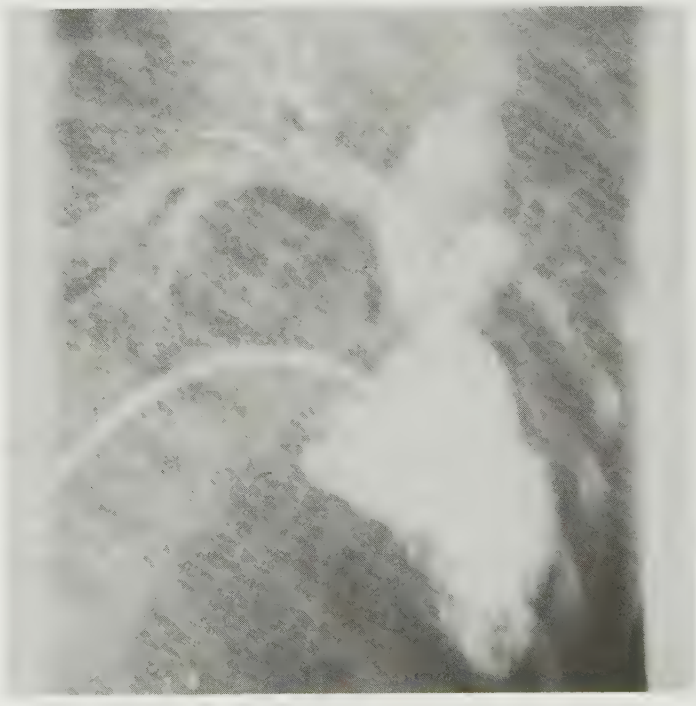

Fig. 67–5. Elongated right anterior oblique view demonstrating right ventricular outflow to truncus with distal filling of aorta and pulmonary arteries. (Angiogram courtesy of Dr. L.M. Bargeron, University of Alabama.)

Prior to 1968, the only surgical palliation available for truncus arteriosus was pulmonary artery banding. The evolvement of radical corrective surgery for truncus arteriosus began with Lillehei et al. when it was demonstrated that the right ventricular outflow tract in tetralogy of Fallot could be enlarged with a patch.[35] In 1965, Rastelli used an artificial, valveless pulmonary artery conduit made of pericardium for pulmonary atresia.[36] Rastelli et al., in 1967, experimentally used an ascending aorta and aortic valve homograft to establish right-ventricular–to–pulmonary-artery flow.[37] In 1968, McGoon et al. used this method for the first successful correction of truncus arteriosus.[38] Later it was found that homografts tended to calcify and become stenotic. In 1973, Malm used an artificial pulmonary trunk of Dacron containing a valve xenograft.[39]

The surgery for primary repair of truncus is based on the original techniques of Rastelli and McGoon.[30,36] The pulmonary trunk is initially incised and separated from the truncus artery. The suture line in the truncus artery is completed and the distal end of the pulmonary trunk is prepared for the conduit. A vertical right ventriculotomy is made to expose the VSD. The VSD is closed by suturing a Dacron patch to the edges of the septal defect in such a way to incorporate the truncal valve into the left ventricular outflow tract. The aortic homograft valved conduit is then interposed between the right ventriculotomy and the pulmonary trunk. Some refinements in technique have been used for repair of types 2 and 3 of Collett and Edwards, such as complete division of the trunk root with primary closure with absorbable suture and isolation of the pulmonary orifice as a button to which the valved conduit is attached.[40,41] Some authors advocate the use of valveless conduits in neonates as a primary repair.[42] Replacement of the conduit is later necessary because of body growth, or pseudointima proliferation. Early primary repair should be considered a two-stage procedure with subsequent conduit replacement.

Primary repair in young infants without fixed alveolar resistance has been achieved by Ebert with the remarkably low mortality rate of 11%. There were no deaths in Ebert's 55 patients requiring conduit replacement.[28]

Twelve percent of patients with truncus arteriosus have a single pulmonary artery. Modified criteria for determining operability are necessary for this subgroup.[31] In truncus with two pulmonary arteries in parallel, the total pulmonary arteriolar resistance is expressed by the following equation:

$$\frac{1}{R_T} = \frac{1}{R_L} + \frac{1}{R_R}$$

in which R_T is the total pulmonary resistance; R_L is the left lung resistance, and R_R is the right lung resistance. This calculation of total pulmonary resistance correlates well with histological arteriolar changes. However, in truncus with unilateral absence of a pulmonary artery the following hemodynamic situation would apply:

$$\frac{1}{R_T} = \frac{1}{R_L} \text{ or } \frac{1}{R_R}$$

By assuming the entire pulmonary blood flow is through the lung with the connected pulmonary artery, Mair[27] postulates that the R_L or R_R should be halved. The calculated resistance by this method correlates well with histologic arteriolar changes in patients with unilateral absence of a pulmonary artery and truncus.

After diagnosis of truncus arteriosus, the challenge to the cardiologist is to determine the optimum time for surgical intervention. Stabilization of the hemodynamics and maturation and growth of the infant need to be balanced with the potential of rapid cardiac deterioration and/or potential for pulmonary hypertension. By surgically correcting infants at 6 months or earlier, persistent pulmonary hypertension can be prevented. The exception to this may be in those infants with a single pulmonary artery; however, the only chance for these infants to avoid persistent pulmonary hypertension is surgery under 6 months of age.[31] Not only is the cardiologist challenged by timing the corrective surgery initially, close followup and deliberation is necessary to determine the optimal timing for conduit replacement.

The continued advances in surgical therapy for truncus arteriosus in the last two decades have been exciting. A lesion previously considered inoperable now is surgically correctable. The refinements in the diagnosis and treatment of truncus arteriosus continues to make treatment of this lesion a most interesting challenge to the physician.

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CHAPTER 68

Ebstein's Anomaly of the Tricuspid Valve

Co-burn J Porter

On June 28, 1864, a 19-year-old laborer was admitted to All Saints' Hospital in Breslau, Poland because of shortness of breath and palpitations.[1] He was quite emaciated, had pronounced cyanosis and marked jugular venous pulsations, and was suspected of having congenital heart disease. Without any treatment, he died a week later, and shortly thereafter a postmortem examination was performed by Dr. Wilhelm Ebstein. Doctor Ebstein found three cardiac abnormalities: 1) a severe malformation of the tricuspid valve, 2) absence of a thebesian valve, and 3) a patent foramen ovale. He recognized that the most important abnormality was that of the tricuspid valve. He published his case report in the *Archiv fur Anatomie, Physiologie und wissenschaftliche Medicin* of January 12, 1866,[2] emphasizing the circulatory disturbances caused by the abnormal tricuspid valve and explaining the genesis of the systolic and diastolic murmurs during life. In 1900, William G. MacCallum, an assistant professor of pathology at Johns Hopkins University, described a museum specimen that appeared to be identical to Ebstein's case: this was the first case to appear in the English literature.[3] In 1927, Alfred Arnstein published the fourteenth case report and concluded that this abnormality of the tricuspid valve should be called ''Ebsteinsche Krankheit'' (Ebstein's disease).[4]

DEFINITION OF LESION

Ebstein's anomaly is a congenital cardiac abnormality in which the tricuspid valve leaflets do not attach normally to the tricuspid valve annulus. The effective tricuspid valve orifice is displaced apically into the right ventricle, near the junction of the inlet and trabecular parts of the right ventricle. There are additional abnormalities of the atrioventricular sulcus, valve leaflet tissue, and structure and internal morphology of the right ventricle. Ebstein's anomaly affects almost exclusively the tricuspid valve (very rare cases of the mitral valve), which is normally the right atrioventricular valve, but the left atrioventricular valve can be affected in cases of congenitally corrected transposition.

ANATOMY[5]

Displacement of Tricuspid Valve Leaflets

Only the septal and posterior (inferior) leaflet attachments are displaced (Fig. 68–1). The commissure between the two leaflets is the point of maximum displacement and is at the posterior border of the ventricular septum. These two leaflets are quite dysplastic and of variable size. In the majority of hearts, the leaflets are truly displaced, and in a smaller percentage the leaflets are extensively adherent to the ventricular wall.

Anterior Leaflet

The anterior leaflet is not displaced but is enlarged (''sail-like'') and has abnormal fibrous strands running through it. This leaflet is abnormally attached posteroinferiorly to the ledge between the inlet and the trabecular portions of the right ventricle.

Atria and Atrioventricular Sulcus

The right atrium is usually quite dilated, and the right atrioventricular junction is enlarged circumferentially. The valve of the inferior vena cava (eustachian valve) is often very prominent.

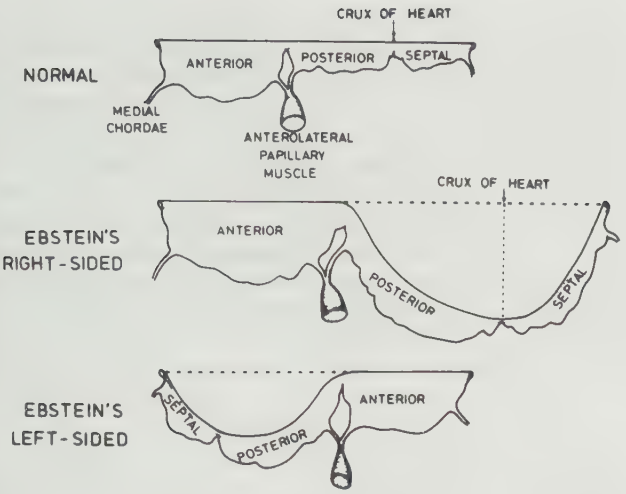

Fig. 68–1. Tricuspid valve opened out to show leaflets in a single plane. In both right-sided and left-sided Ebstein's anomaly, point of maximum displacement is at commissure between septal and posterior leaflets. This commissure is normally situated at crux of heart. (From Anderson, K.R., et al.: Morphologic spectrum of Ebstein's anomaly of the heart: a review. Mayo Clin. Proc., *54*:174, 1979. By permission of Mayo Foundation.)

Right Ventricle

Because of the displaced tricuspid valve, the right ventricle is divided into two parts: the inlet portion (''atrialized'' ventricle) and the trabecular and outlet portions (functional ventricle). The atrialized ventricle usually has a thinner wall than the functional right ventricle. Pathologic studies in patients with dilation of the functional right ventricle have shown a thinning of the wall, with an absolute decrease in the number of myocardial fibers. Uhl's anomaly of the right ventricle may closely resemble Ebstein's anomaly, but there is no abnormality of the tricuspid valve in the former.[6]

Imperforate Ebstein's Anomaly

Approximately 10% of hearts with Ebstein's anomaly have an imperforate tricuspid valve. In this situation, the anterior leaflet totally blocks the atrialized ventricle from the functional portion. This has been referred to also as ''Ebstein's anomaly with tricuspid atresia.''

Coronary Arteries

In the usual form of Ebstein's anomaly, the coronary arteries are normal except for the fact that the right coronary artery may be displaced superiorly and posteriorly (coursing in the atrioventricular sulcus) because of an aneurysmally dilated atrialized ventricle.

Conduction Tissue

Limited studies have been performed on the specialized conduction tissue in hearts with Ebstein's anomaly.[5,7] The sinoatrial node appears to be normally positioned as is the proximal part of the atrioventricular conduction tissue. However, various abnormalities of the right bundle branch have been reported. It may a) be located superficially in the subendocardium of the atrialized ventricle; b) fan out in a fashion similar to the normal left bundle branch; c) give off small communications high to the right side of the septum; and d) be encased in dense, fibroelastic tissue. In addition, accessory atrioventricular pathways have been reported bridging the right atrioventricular sulcus and giving rise to the Wolff-Parkinson-White pattern on the electrocardiogram.[7] During normal embryogenesis, the AV valve leaflets and tensor apparatus are formed by delamination of the inner layers of the inlet zone of the ventricles. In Ebstein's anomaly, the AV junction is juxtaposed to the inlet zone, such that abnormal delamination and displacement of the junction of the inlet and trabecular septum could arrest the development of the right sided AV annulus.

Associated Anomalies

A patent foramen ovale or true atrial septal defect is found in virtually all patients with Ebstein's anomaly. Pulmonary stenosis or atresia is found in a small perecentage of patients. A ventricular septal defect is found rarely.

Left Ventricle

Histology of the left ventricle in patients age 9 to 40 years with Ebstein's anomaly has shown variable large areas of fibrosis, hypertrophy, and nonspecific dysplasia.[8] All of these findings are consistent with the left ventricular dysfunction seen at catheterization or on two-dimensional echocardiography.

EMBRYOLOGY

The tricuspid valve leaflets and chordae are formed from the interior of the embryonic right ventricular myocardium by undermining the inlet zone of the ventricular wall (''delamination'').[9] Initially muscular, the leaflets and chordae later become fibrous. The anterior leaflet is formed very early in development, but the posterior and septal leaflets are formed much later (in the 3- to 4-month-old fetus) (Fig. 68–2). In Ebstein's anomaly, the inferior and septal leaflets insert at the junction of the inlet and trabecular portions, suggesting an arrest in the delamination process. The

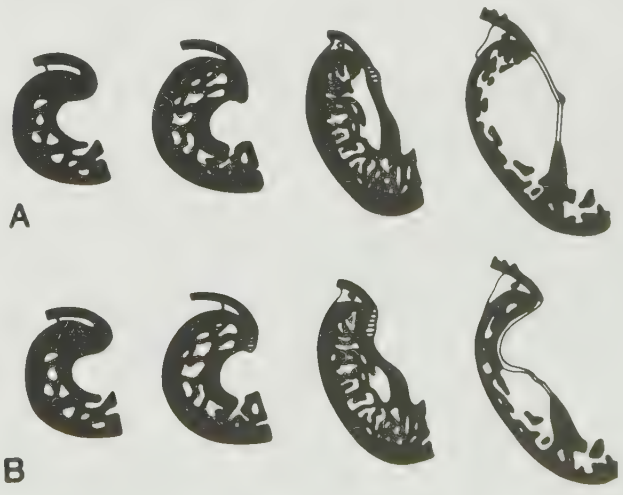

Fig. 68–2. (A) Formation of normal atrioventricular valve cusp. (B) Ebstein's anomaly. (From Van Mierop, L.H.S., and Gessner, I.H.: Pathogenetic mechanisms in congenital cardiovascular malformations. Prog. Cardiovasc. Dis., *15*:67, 1972. By permission of Grune & Stratton.)

anterior leaflet is also formed from tissue at the junction of the inlet and trabecular zones. In the imperforate or highly stenotic types of Ebstein's anomaly, the anterior leaflet forms the dividing membrane and may be entirely muscular.

EPIDEMIOLOGY, ETIOLOGY, AND GENETICS

Ebstein's anomaly is a relatively rare congenital heart defect, found in 1 of 1000 autopsies of patients with congenital cardiac lesions[10]; the suggested incidence figure is 1 per 210,000 live births.[11] This defect is believed to constitute less than 1% of all congenital heart defects.[11] Of 2251 infants with cardiac disease who qualified for entry into the New England Regional Infant Cardiac Program, 13 had Ebstein's anomaly (0.5%).[12] There are equal numbers of males and females with Ebstein's disease.[13,14] Lithium has been implicated as a possible etiologic agent.[15] The majority of instances are sporadic, but familial cases have been reported. There is a difference of opinion as to whether there is a hereditary basis for transmission.[16,17]

PATHOPHYSIOLOGY

The broad spectrum of pathologic findings in Ebstein's anomaly produces the variable hemodynamic manifestations. The pathophysiologic changes are related to several factors: a) degree of tricuspid valve incompetence or, more rarely, stenosis; b) presence of a true atrial septal defect or patent foramen ovale; c) degree of right ventricular dysfunction; and d) amount of left ventricular dysfunction. To a lesser degree, the pathologic substrates predisposing to tachyarrhythmias produce an additional dimension contributing to the pathophysiology.

Because of tricuspid valve incompetence or stenosis, there is a reduced volume of blood in the right ventricle to be ejected into the pulmonary circulation and a larger volume of blood in the right atrium. This larger volume of blood in the right atrium contributes to right atrial distention and, in the presence of an atrial septal defect or patent foramen ovale, results in right-to-left shunting at the atrial level. In addition, because of ventricular dysfunction in an already small, functional right ventricle, during ventricular systole pulmonary forward flow can be impaired leading to further regurgitation and right-to-left shunting; during ventricular diastole true right ventricular filling can be impaired because of reduced ventricular compliance. With increasing amounts of right-to-left shunting, there will be increasing cyanosis and higher levels of polycythemia. In patients with Ebstein's anomaly, decreased functional capacity (measured by New York Heart Association [NYHA] classification) was related to a) a small functional right ventricle and large atrialized right ventricle, b) valve leaflet abnormalities such as extreme displacement or absence of the septal leaflet and degree of displacement or tethering of the anterior leaflet, and c) the aneurysmal dilation of the right ventricular outflow tract.[18]

Although the primary focus in patients with Ebstein's anomaly has been on right-sided structures, there have been an increasing number of reports of left-sided abnormalities, specifically in left ventricular size, shape, and function,[8,19,20] primarily due to diastolic bowing of the interventricular septum toward the left ventricular free wall. Radionuclide scans and cineangiograms have shown impaired left ventricular function at rest in unoperated patients.[8,19,20] With exercise, most unoperated patients show an appropriate increase in left ventricular ejection fraction due to a reduced end-systolic volume and unchanged end-diastolic volume.[20]

The infant with Ebstein's anomaly poses an additional problem. In all infants immediately after birth, the pulmonary resistance is elevated and decreases fairly rapidly in the first days of life. However, in the infant with Ebstein's anomaly the combination of tricuspid regurgitation and elevated pulmonary resistance can lead to right heart failure and a significant right-to-left shunt. These infants can be quite cyanotic and present a therapeutic dilemma until the pulmonary resistance begins to decrease and the pulmonary flow increases.

CLINICAL FEATURES

History

It is usual for a patient with Ebstein's anomaly to present in the newborn period. In general, these infants have severe cyanosis as the predominant sign; less frequently they may have a murmur or supraventricular tachycardia. Beyond the newborn period the presentation is more variable (Table 68–1). Although some older patients are without symptoms, the majority have dyspnea (or fatigability), cyanosis, or palpitations (or true tachycardia).[13,14,21,22] In these patients, low arterial oxygen tensions stimulate the carotid bodies and cause increased ventilation. In addition, inadequate perfusion of exercising muscles may provoke reflex ventilatory stimulation. Palpitations are caused by single or multiple premature atrial or ventricular extrasystoles, or both; prolonged palpitations are due to paroxysmal tachyarrhythmias, generally supraventricular in origin, but occasionally ventricular. Palpitations in a cyanotic child should raise the possibility of Ebstein's anomaly.

Physical Findings

At the Mayo Clinic, many older children and adults have been referred for evaluation. In our series, the mean age at diagnosis

Table 68–1. Clinical Findings at the Time of Diagnosis of Ebstein's Anomaly in 67 Patients

	Patients	
Finding	*No.*	*%*
Dyspnea	40	60
Cyanosis	41	61
Palpitations	8	12
Edema	7	10
Functional class (NYHA)		
I	13	19
II	24	36
III	23	34
IV	7	11
Electrocardiogram abnormal	67	100
Chest roentgenogram abnormal	67	100
No cardiomegaly	5	7
Cardiomegaly	62	93

From Giuliani, E.R., Fuster, V., Brandenburg, R.O., and Mair, D.D.: Ebstein's anomaly: the clinical features and natural history of Ebstein's anomaly of the tricuspid valve. Mayo Clin. Proc., *54*:163, 1979. By permission of Mayo Foundation.

was 14.1 years (Fig. 68–3)[14]; the oldest patient presented with severe tricuspid incompetence and congestive heart failure at 79 years.[23] Growth and development are generally normal. Cyanosis and digital clubbing are present in patients with associated right-to-left shunt. Many have an unusual facial coloration described as "violaceous hue," "flushed," "florid," "red cheeked," or "malar flush."[22] Usually, these patients have at least mild polycythemia. Asymmetry of the chest with prominence of the left side is a frequent finding; however, an overactive precordium is rarely found. Arterial and venous pulsations are normal usually, even in the presence of tricuspid insufficiency. The jugular venous pulsations may not have the large "V" wave because of poor transmission of the venous pulse wave in the presence of a dilated, compliant right atrium.

Generally, auscultation is one of the first findings alerting one to the diagnosis of Ebstein's anomaly. There is a multiplicity of sounds and murmurs that are so characteristic as to "stand out" even to the untrained ear. Occasionally the heart sounds are soft, but usually they are of normal intensity. The first heart sound is widely split, due to delayed closure of the abnormal tricuspid valve. The second heart sound is also widely and persistently split due to late closure of the pulmonic valve, believed to be due to right bundle branch block. Ventricular filling sounds (S_3 or S_4, or both) are common and contribute to the multiplicity of heart sounds. Because of so many heart sounds, one perceives a "gallop" or "quadruple" rhythm or cadence quality, which is fairly easily recognized. A holosystolic murmur (grade 2 to 4 over 6) is found along the left sternal border—a manifestation of tricuspid regurgitation. Frequently, in the same location, there are diastolic murmurs of low intensity as a result of anterograde flow across the tricuspid valve. All murmurs tend to vary with respiration, increasing with inspiration.

Electrocardiogram

The electrocardiogram is usually abnormal and helps to confirm the clinical diagnosis (Table 68–1, Fig. 68–4). Although sinus rhythm is usually present, atrial fibrillation can be found in a few patients. In any large series, one-third to one-half of the patients have prolonged P-R intervals, and one-fourth to three-fourths meet criteria for right atrial enlargement ("himalayan" P waves).[14,22] The QRS axis in the frontal plane occasionally shows right-axis deviation. Most patients have right bundle branch block and many have low-voltage QRS complexes in the right precordial leads. Right ventricular hypertrophy is extremely uncommon.

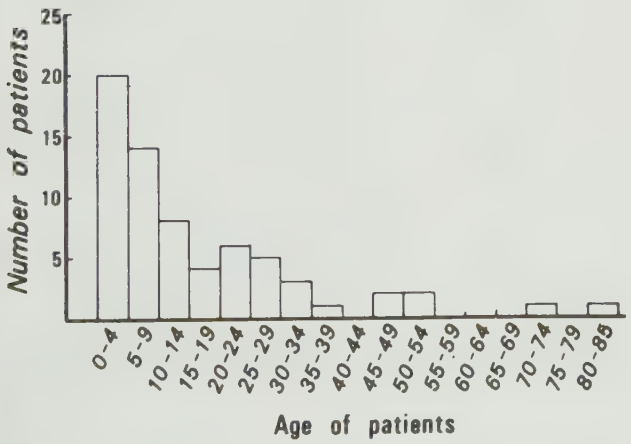

Fig. 68–3. Age distribution of 67 patients with proven Ebstein's anomaly of tricuspid valve. Age at time of diagnosis is given. (From Giuliani, E.R., Fuster, V., Brandenburg, R.O., and Mair, D.D.: Ebstein's anomaly: the clinical features and natural history of Ebstein's anomaly of the tricuspid valve. Mayo Clin. Proc., *54*:163, 1979. By permission of Mayo Foundation.)

From 4 to 26% of patients with Ebstein's anomaly have the Wolff-Parkinson-White pattern, virtually always type B (Fig. 68–5).[14,22,24] This is due to an accessory atrioventricular connection. Several resting or exercise electrocardiograms or 24-hour ambulatory electrocardiograms may have to be examined to find the characteristic electrocardiographic pattern. Occasionally, the pattern is transient or intermittent.[25–27] The absence of anterograde pre-excitation does not indicate that the accessory connection is no longer present or that the patient is no longer susceptible to tachycardia. The patient may still have retrograde conduction allowing for reentry tachycardia to occur. Patients with Ebstein's anomaly, a normal P-R interval, and a delta wave may have Wolff-Parkinson-White, but extremely delayed conduction through the right atrium; if there is coexistent left-axis deviation, there may be an accessory nodoventricular connection (Mahaim fiber).[28]

Arrhythmias in the unoperated patient with Ebstein's anomaly are common.[29] Of 52 patients who underwent evaluation for surgery at the Mayo Clinic, 41 (79%) had either documented arrhythmias or history of palpitation, near syncope, or syncope. Of 34 patients with electrocardiographic documentation of one or more arrhythmias, 18 had paroxysmal supraventricular tachycardia, 10 had paroxysmal atrial fibrillation or flutter, 13 had ventricular arrhythmias (7 frequent ventricular premature complexes and 5 nonsustained ventricular tachycardia), and 3 had atrioventricular block (2 complete AV block and 1 Mobitz II second degree). Of the 13 patients with ventricular arrhythmias, 5 had, in addition, paroxysmal supraventricular tachycardia, 4 had paroxysmal atrial fibrillation or flutter, and 1 had complete AV block. The patients with arrhythmias or symptoms compatible with arrhythmia were significantly older than patients without symptoms or arrhythmias.

Chest Radiograph

The cardiac size may vary from near normal to the extreme cardiomegaly that is fairly typical of Ebstein's anomaly. The typical contour is found in most cases and consists of a "balloon-shaped" enlarged heart with a narrow base reminiscent of that seen with a pericardial effusion (Fig. 68–6). The dilated right atrium is responsible for most of the enlarged cardiac silhouette. In the PA view, the right atrium produces a significant convexity of the right heart border, whereas in the lateral view the right atrium may fill the entire retrosternal space. The convex left heart border is due primarily to dilation of the right ventricular outflow tract. The convexities of both left and right heart borders produce a rather characteristic "globular" cardiac silhouette. In cyanotic patients with a right-to-left shunt, the pulmonary vascularity is decreased; otherwise it is usually normal. In the newborn period it is not unusual for the heart to have normal size and shape. This may confuse the clinical diagnosis.

Echocardiography

At the Mayo Clinic, echocardiography has become the procedure of choice for the diagnosis and preoperative assessment of

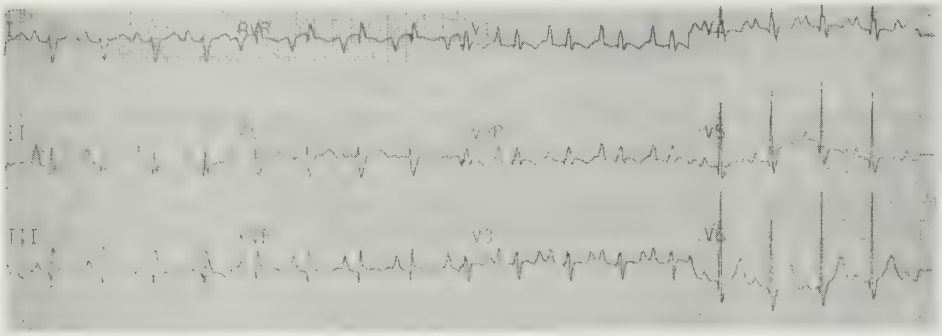

Fig. 68–4. ECG from 15-year-old boy with Ebstein's anomaly. Note prominent P wave, prolonged AV conduction, and delay in right ventricular conduction. (From Driscoll, D.J., Fuster, V., and McGoon, D.C.: Congenital heart disease in adolescents and adults. I. Ebstein's anomaly of the tricuspid valve. *In* Cardiology: Fundamentals and Practice. Edited by R.O. Brandenburg, V. Fuster, E.R. Giuliani, and D.C. McGoon. Chicago, Year Book Publishers, 1987, pp. 1459–1469. By permission of Mayo Foundation.)

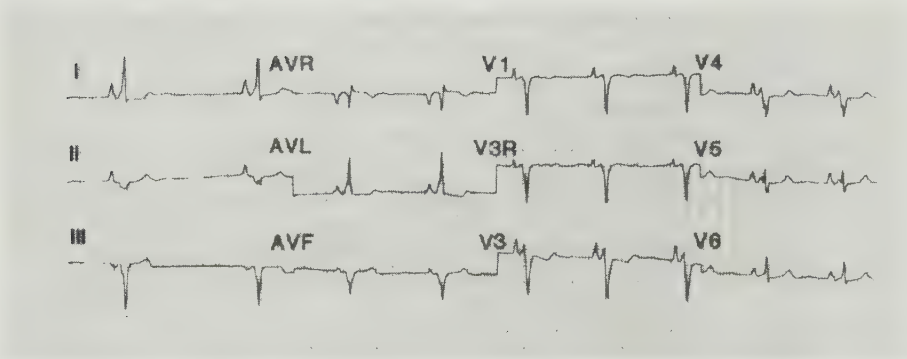

Fig. 68–5. Electrocardiogram of 13-year-old girl with Ebstein's anomaly and pre-excitation shows evidence of right atrial enlargement and Wolff-Parkinson-White syndrome (type B with delta waves in leads I, AVL, and V4-6). (From Porter, C.J., and Holmes, D.R.: Preexcitation syndromes associated with congenital heart disease. *In* Cardiac Preexcitation Syndromes. Edited by D.G. Benditt and D.W. Benson. Boston, Martinus Nijhoff, 1986, pp. 289–301. By permission of the publisher.)

Fig. 68–6. Chest radiograph from an 11-year-old male shows a narrow base and moderate generalized cardiomegaly. The prominent right heart border is a result of the enlarged right atrium. Dilatation of the right ventricular outflow tract produces displacement of the upper left cardiac border. The pulmonary vascular markings are normal to somewhat decreased.

patients with Ebstein's anomaly. Initially only M-mode echocardiography was available for evaluation. Features of Ebstein's anomaly found with M-mode echocardiography included: a) ability to record the anterior tricuspid leaflet farther to the left of the left sternal border than in normals and b) abnormally prolonged interval between the closure points of the tricuspid and mitral valve echoes.[30] The most reliable single M-mode criterion is the relationship of mitral valve closure to tricuspid valve closure. Normally the tricuspid valve closes within 30 to 50 milliseconds after the mitral valve.[30,31] If the tricuspid closure is more than 50 milliseconds after the valve closure, the diagnosis of Ebstein's anomaly should be strongly considered (Fig. 68–7).[14] Abnormal activation of the right ventricle (i.e., right bundle branch block) is not responsible for the prolonged mitral-tricuspid closure interval.[32]

With the advent of two-dimensional echocardiography, the diagnosis of Ebstein's anomaly has become easier to make.[33–35] Real-time two-dimensional imaging has provided several reliable features found in patients with Ebstein's anomaly (Fig. 68–8): a) apical displacement of the septal leaflet of the tricuspid valve (virtually all patients), b) displacement of the anterior leaflet (uncommon), c) leaflet tethering to subjacent myocardium of either the septal or the large anterior leaflet (specific for Ebstein's), d) absence of septal tricuspid leaflet (uncommon), e) elongation of the anterior leaflet (characteristic of Ebstein's), f) increased tricuspid valve annulus dimension (most), g) increased total right ventricular cavity size (nonspecific), h) aneurysmally dilated right ventricular outflow tract (infrequent), i) exaggerated tricuspid valve motion (virtually all), j) reduced left ventricular contractility (occasionally), and k) mitral valve prolapse (infrequent).[18]

In normal hearts the septal leaflet of the tricuspid valve inserts more apically than the septal portion of the anterior mitral leaflet. Therefore, certain criteria had to be developed to characterize

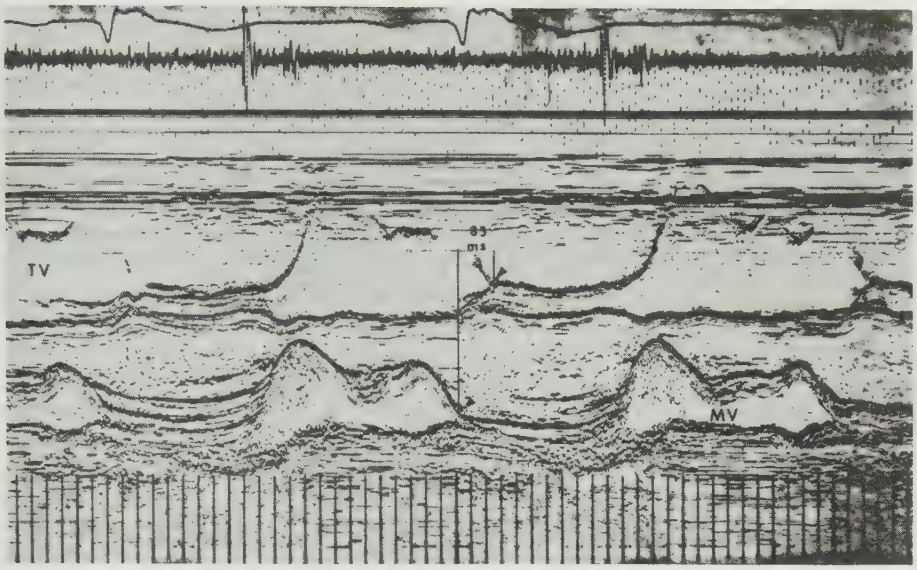

Fig. 68–7. Echocardiogram in cyanotic 29-year-old man with Ebstein's anomaly and cardiac failure. Note 85-ms interval between mitral and tricuspid valve closure. *TV* = tricuspid valve; *MV* = mitral valve. (From Giuliani, E.R., Fuster, V., Brandenburg, R.O., and Mair, D.D.: Ebstein's anomaly: the clinical features and natural history of Ebstein's anomaly of the tricuspid valve. Mayo Clin. Proc., *54*:163, 1979. By permission of Mayo Foundation.)

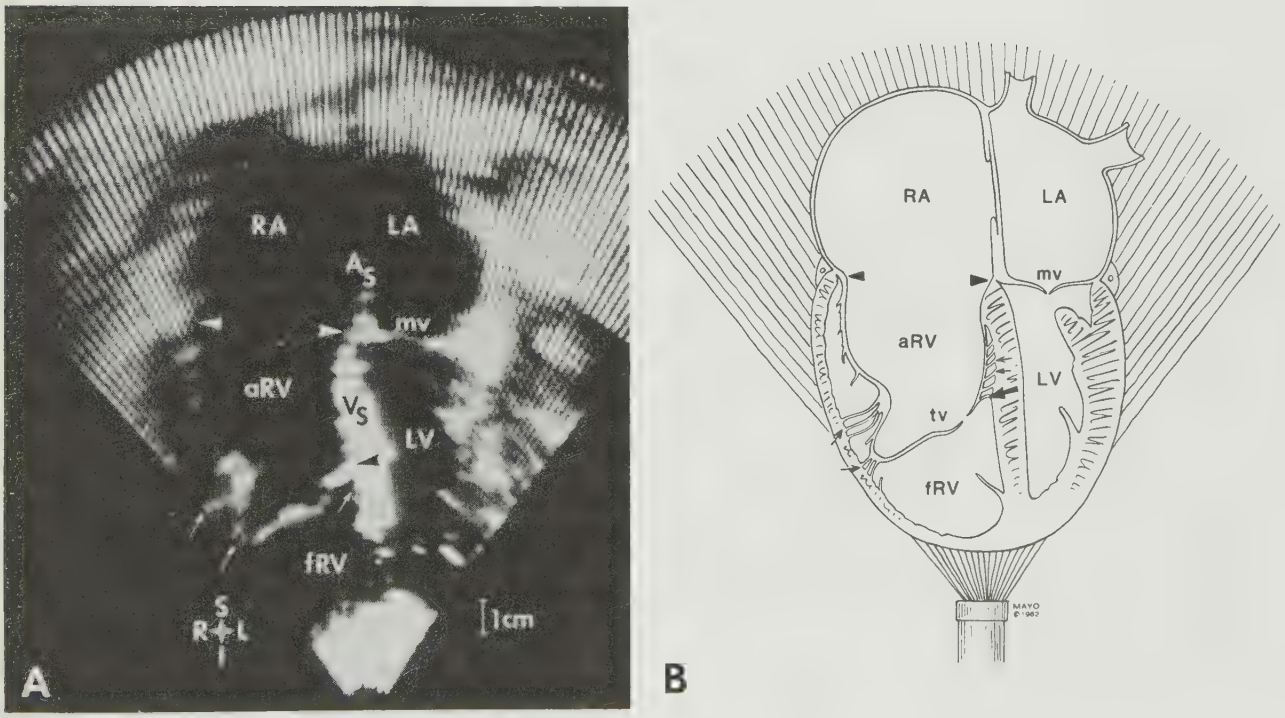

Fig. 68–8. Two-dimensional echocardiogram, typical four-chamber view, in a patient with Ebstein's anomaly. Note that septal tricuspid valve (*tv*) leaflet was displaced into right ventricle (*large black arrow*) and thus formed atrialized right ventricle (*aRV*). Anterior tricuspid leaflet was elongated, and it originated from true tricuspid annulus (*top arrowheads*). Both leaflets were tethered to underlying myocardium (*small arrows*). Tricuspid annulus and right atrium (RA) were dilated. *AS* = atrial septum; *fRV* = functional right ventricle; *I* = inferior; *L* = left; *LA* = left atrium; *LV* = left ventricle; *mv* = mitral valve; *R* = right; *S* = superior. (Part A, from Shiina, A., et al.: Two-dimensional echocardiographic-surgical correlation in Ebstein's anomaly: preoperative determination of patients requiring tricuspid valve plication vs replacement. Circulation, *68*:534, 1983. By permission of the American Heart Association. Part B, from Shiina, A., et al.: Two-dimensional echocardiographic spectrum of Ebstein's anomaly: detailed anatomic assessment. J. Am. Coll. Cardiol., *3*:356, 1984. By permission of the publisher.)

abnormal apical displacement of the septal leaflet of the tricuspid valve. At the Mayo Clinic, a value greater than 8 mm/m^2 of the patient's body surface area for the distance from the tricuspid annulus to the distal point of septal leafet attachment in systole is consistent with a diagnosis of Ebstein's anomaly.[18] Other authors have reported that the "critical difference" for discrimination is greater than 15 mm in children (<14 years old) and greater than 20 mm in adults.[36] By using two-dimensional echocardiographic techniques, the degree of malformation of the tricuspid valve can be determined and has been correlated with functional capacity and with whether or not surgical repair can be accomplished without the use of a prosthetic valve.[18,37,38] In addition, associated defects such as ventricular septal defects and pulmonary stenosis can be detected by two-dimensional echocardiography.

Recently Doppler and color-flow echocardiography have enhanced the noninvasive evaluation of patients with Ebstein's anomaly. Hemodynamic alterations such as valve regurgitation and intracardiac shunting can be determined in a more sensitive, qualitative fashion. With the use of these combined echocardiographic techniques, hemodynamic cardiac catheterizations are no longer necessary for patients with Ebstein's anomaly evaluated at the Mayo Clinic.

Exercise Testing

Exercise testing has become a part of the routine noninvasive studies used to evaluate patients with Ebstein's anomaly, both in the unoperated and postoperative state. Studies performed at the Mayo Clinic before and after surgery have described several interesting findings.[39,40] In unoperated patients, indices of exercise tolerance (work, exercise duration, maximal oxygen uptake) are significantly reduced. However, in postoperative patients, these indices approach the lower limit of normal. In four patients tested both preoperatively and postoperatively, three had increased exercise tolerance as measured by maximal oxygen uptake. Systemic arterial blood oxygen saturation is significantly lower at rest and during exercise in unoperated patients compared with postoperative patients. In the unoperated patient there is a significant positive correlation between maximal oxygen uptake achieved (exercise tolerance) and both rest and exercise systemic arterial oxygen saturation. The majority of unoperated patients with intact atrial septum had rest cardiac outputs (acetylene-helium rebreathing technique) below the normal mean, whereas the majority of postoperative patients had rest cardiac outputs above the normal mean. Exercise cardiac outputs were low in all of the unoperated patients with intact atrial septum and in the normal range in all the postoperative patients except one. Patients with an atrial septal defect and right-to-left shunting demonstrated excessive ventilation at rest and during exercise. In these patients a right-to-left shunt is a strong stimulus to increase ventilation.

CARDIAC CATHETERIZATION

Hemodynamics

In the early days of intracardiac investigation, it became evident that patients with Ebstein's anomaly had an increased risk for morbidity or mortality from cardiac catheterization. Some physicians stated that these patients should not undergo this procedure. However, concerns about the safety of cardiac catheterization in these patients have been lessened by modern techniques of monitoring the patient's hemodynamic status during the study and the availability of effective treatment for arrhythmias provoked by catheter manipulation.

Ebstein's anomaly is characterized by moderate elevation of the right atrial pressure, most often with a dominant V wave and steep Y descent. If, however, the right atrium is massively dilated, the atrial pressure may be normal in spite of severe tricuspid regurgitation. Most often the right ventricular pressures are normal, but in some the end-diastolic pressure may be elevated. Generally the pulmonary artery pressure is normal, but it may be decreased in those with severe tricuspid regurgitation and right-to-left shunting. In those with an atrial septal defect, right-to-left shunting results in systemic arterial desaturation. Right-to-left shunting can be demonstrated also by intracardiac dye dilution curves with injection into the inferior or superior vena cava showing early appearing dye at the systemic arterial sampling site. Of historical significance is a technique of simultaneously recording the intracavitary pressure and intracardiac electrogram tracing. When a catheter with an opening and an electrode at the tip was positioned in the atrialized portion of the right ventricle, the pressure tracing recorded was atrial, but the electrogram showed ventricular activity.

Angiocardiography

Right ventricular angiocardiography is usually diagnostic of Ebstein's anomaly, except in the mildest forms. In the AP projection, contrast injection in the right ventricle will demonstrate tricuspid regurgitation, a large sail-like anterior tricuspid leaflet, and frequently a distinct notch at the inferior cardiac border to the left of the spine (Figs. 68–9 and 68–10). The notch is the site of the abnormal attachment of the displaced anterior leaflet. Frequently a "trilobed" appearance to the right-sided structures occurs as a result of contrast medium outlining the enlarged right atrium, atrialized ventricle, and the outflow portion of the functional ventricle. The presence of associated defects can be demonstrated by angiocardiography.

In a cyanotic newborn with Ebstein's anomaly, injection of contrast medium in the right ventricle may show tricuspid regurgitation and little or no contrast medium in the pulmonary artery. This suggests anatomic obstruction to the right ventricular outflow tract. However, this same finding may occur without anatomic obstruction if the pulmonary resistance is elevated. Patency of the right ventricular outflow tract should be established by other techniques, such as catheter advancement through a patent pulmonary valve or injection of contrast medium in the ductus arteriosus to show contrast medium filling the main pulmonary artery and regurgitating into the right ventricle.

Electrophysiology

Because of the occurrence of tachyarrhythmias or symptoms compatible with tachyarrhythmias in patients with Ebstein's anomaly, electrophysiologic evaluation has been performed in these patients with increasing frequency.[41,42] At the Mayo Clinic echocardiographic evaluation of anatomy has become so accurate that the only indication for a cardiac catheterization is to evaluate any arrhythmias or suspected arrhythmias. Twenty-three patients with Ebstein's anomaly underwent electrophysiologic testing at the Mayo Clinic between 1974 and 1984.[41] All patients were evaluated because of recurrent symptomatic tachycardia or as a part of their

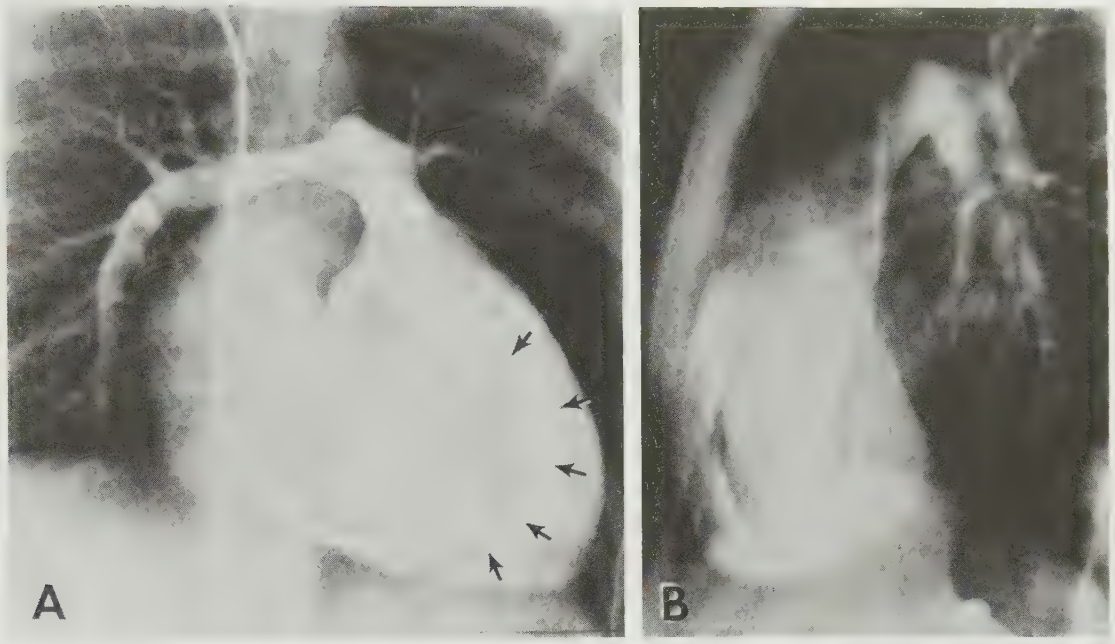

Fig. 68–9. (A) Anteroposterior and (B) lateral views of right ventriculogram in 21-year-old woman. Anteroposterior view shows large "sail-like" anterior leaflet (*arrow*) displaced well to left of spine. Severe tricuspid incompetence is evident. Lateral projection displays pronounced anterior displacement of abnormal anterior tricuspid leaflet. (From Giuliani, E.R., Fuster, V., Brandenburg, R.O., and Mair, D.D.: Ebstein's anomaly: the clinical features and natural history of Ebstein's anomaly of the tricuspid valve. Mayo Clin. Proc., *54*:163, 1979. By permission of Mayo Foundation.)

Fig. 68–10. Angiocardiogram in 25-year-old acyanotic man. Note "notch" at inferior cardiac border, well to left of spine. (From Giuliani, E.R., Fuster, V., Brandenburg, R.O., and Mair, D.D.: Ebstein's anomaly: the clinical features and natural history of Ebstein's anomaly of the tricuspid valve. Mayo Clin. Proc., *54*:163, 1979. By permission of Mayo Foundation.)

preoperative assessment before tricuspid valvuloplasty or valve replacement. Of the 23 patients, 12 had both Ebstein's anomaly and pre-excitation and underwent valve surgery with ablation of the accessory atrioventricular connections. Eleven of these 12 patients had a history of tachycardia before the electrophysiologic study.

In the patients with pre-excitation studied preoperatively at the Mayo Clinic, the average PA interval was 37 msec (range, 15 to 63 msec) and the average AH interval was 86 msec (range, 70 to 120 msec); half of the patients had enhanced atrioventricular nodal conduction and 1 patient had dual atrioventricular nodal physiology; 10 accessory pathways were right free-wall and 3 were septal; 1 patient had both a right free-wall and a septal pathway. In the series reported by Smith et al.,[42] 11 patients had a right free-wall pathway, 7 a septal pathway, and 4 had both. During study at the Mayo Clinic, six patients had one mechanism and four patients had two mechanisms for their arrhythmia. Orthodromic reciprocating tachycardia was found in seven patients: four had reentrant tachycardia only and three also had atrial flutter/fibrillation. One patient had reciprocating tachycardia due to reentry within the AV node, one had both intra-atrial reentry tachycardia and atrial flutter/fibrillation, and one had only atrial flutter. No patient had antidromic reciprocating tachycardia or evidence of an accessory nodo- or fasciculoventricular connection. No patient had induction of ventricular tachycardia. All patients in the series by Smith et al. had evidence of orthodromic reciprocating tachycardia; one also was suspected of having antidromic reciprocating tachycardia, three were believed to have an additional accessory nodoventricular or fasciculoventricular pathway, and one had inducible ventricular tachycardia.

NATURAL HISTORY

In 1974, Watson published the result of an international cooperative study of 505 cases collected from 61 centers in 28 countries.[43] Thirty-five were less than 1 year old, 403 were between 1 and 25 years, and 67 were over 25 years. Of the infants, 72% were in heart failure; but in 81% of the older patients, growth and development during infancy were said to have been average or good. Under one year of age there were 16 deaths in 35 patients for a mortality of 45.7 percent. Of the 16 deaths, 15 (94%) were due to congestive heart failure, all in patients less than 6 months old.[43] Of the patients age 1 to 25 years, 71%, and of those over age 25 years, 60%, had little or no disability and were classified as NYHA class I or II. Cardiac catheterizations had been carried out on 363 patients, with 19 cardiac arrests (13 of the 19 died). A paroxysmal tachycardia occurred during the catheterization in 90 patients (25%).

Of the 505 patients, 77 (15.2%) died from their disease. An additional 31 who had surgical treatment for Ebstein's anomaly died (54.4% surgical mortality). There is an initial high mortality from congestive heart failure in the first few months of life. Between the ages of 1 and 25 years, 50 (12.4%) of the 403 patients died from their disease. Half of the deaths were due to congestive heart failure and 20% of them were sudden deaths, presumably due to an arrhythmia. Over 25 years, there were 11 deaths (16.4%) in 67 patients.

Watson reported high mortalities with surgical treatment. For patients between ages 1 and 15 years, there was a 64% mortality for palliative procedures, such as Glenn or Blalock shunts, and a 56% mortality for definitive surgical treatment, such as insertion of a tricuspid valve prosthesis. In 15 patients over age 15 years who had definitive repair with a prosthesis, there was a 33% mortality. Thus it appeared from this early paper that surgery was not beneficial.

There have been reports of women with mild Ebstein's anomaly becoming pregnant and delivering healthy term infants.[44,45] However, others have reported fetal deaths in mothers who had more significant Ebstein's anomaly.[46,47] After surgical repair, some mothers have had uncomplicated and successful pregnancies.[48]

THERAPY

In Ebstein's anomaly there is a wide spectrum of hemodynamic abnormalities and arrhythmias that occur at various ages; therefore, no dogmatic recommendations can be made; general guidelines can be presented and each case must be judged individually. At one end of the spectrum are patients with mild anatomic abnormalities, relatively normal hemodynamics, and no symptoms, who require only observation and normal precautions to prevent bacterial endocarditis. But beyond this, the anatomic and hemodynamic abnormalities may become important enough to cause symptoms and significantly alter the patient's lifestyle. Medical therapy may be necessary for these patients, but frequently surgical therapy must be considered. The natural history of this congenital heart defect suggests that many patients do well with little or no therapy, but a certain subset requires surgical intervention.

The surgical approach to Ebstein's anomaly has evolved over the past 30 years. In the 1950s, systemic-to-pulmonary artery anastomoses were created to increase pulmonary blood flow. They were not very successful. Better results were obtained with the Glenn shunt, a superior vena cava-to-pulmonary artery connection.[49] In 1958, Hunter and Lillehei[50] tried repositioning the septal and posterior tricuspid valve leaflets, but this had no apparent success. In 1962, Barnard and Schrire[51] successfully replaced the tricuspid valve with a prosthesis; this patient was still alive and doing well 19 years after operation.[52] Reconstruction of the tricuspid valve was attempted in 1969 by Hardy and Roe.[53] At present, three approaches are available for the surgical repair of Ebstein's anomaly: 1) replacement of the valve[8,54–56] with either a mechanical or a "biological" prosthesis, 2) reconstruction of the valve,[53,57] or 3) both replacement and reconstruction.[58]

Drawing from the pioneering efforts by other surgeons, Danielson of the Mayo Clinic developed a "plastic" repair based on construction of a monocusp valve by using the enlarged anterior leaflet of the tricuspid valve (Fig. 68–11).[59] Between April 1972 and January 1982 he performed surgical repair on 42 consecutive patients with Ebstein's anomaly.[57] Of the 42 patients, 34 (81%) had a plastic repair consisting of plication of the free wall of the atrialized portion of the right ventricle, posterior tricuspid annuloplasty, and right atrial reduction. Right ventricular plication and valve replacement with a bioprosthesis were performed in six patients (14%). Two patients (5%) had a previous Glenn procedure and tricuspid valves that could not be reconstructed. In these two patients, the atrialized ventricle was plicated, and the tricuspid valve excised and not replaced. The indications for operation were functional class III or IV (NYHA), progressive cyanosis, paradoxic emboli, or uncontrollable tachyarrhythmias secondary to accessory pathways.

Mair, Danielson, and colleagues[48] provided information on an additional 30 patients. By August of 1984, a total of 72 patients with Ebstein's anomaly had undergone surgical repair at the Mayo Clinic. A plastic reconstruction of the tricuspid valve was possible in 58 patients, 81% of the entire group. In 11 patients (15%) valve replacement (10 Hancock bioprostheses) and right ventricular plication were done. In three patients (4%) with Glenn anastomoses, a Fontan-type arrangement was produced. Nine patients had accessory atrioventricular pathways ablated successfully. There were five deaths in the hospital (7%) and three late sudden deaths. Two deaths in the hospital were caused by documented ventricular fibrillation. Of those dying late, all had large hearts before surgery and significant atrial or ventricular arrhythmias before operation. Followup was available in all surviving patients for at least 2 years, with a mean of 5 years. Eighty-seven percent of the patients were in functional class I or II at followup. Significant improvements in exercise tolerance have been found in patients tested after surgery (see section on Exercise Testing in this chapter).

Because of the success of surgical treatment for certain patients with Ebstein's anomaly, selection criteria have been refined.[48] At the Mayo Clinic, surgery is recommended for the following patients: a) those whose symptoms have deteriorated to place them in NYHA class III or IV; b) those who are still in NYHA class I or II but whose cardiothoracic ratio on the plain chest film has reached 0.65 or greater; c) those with significant cyanosis (an arterial saturation of 80% or less with a hemoglobin of 16 gm or higher) and polycythemia; d) those who have suffered a paradoxical embolus, even if still in NYHA class I or II; and e) those who have an accessory atrioventricular pathway with medically uncontrollable reciprocating tachycardia. Indications for surgery

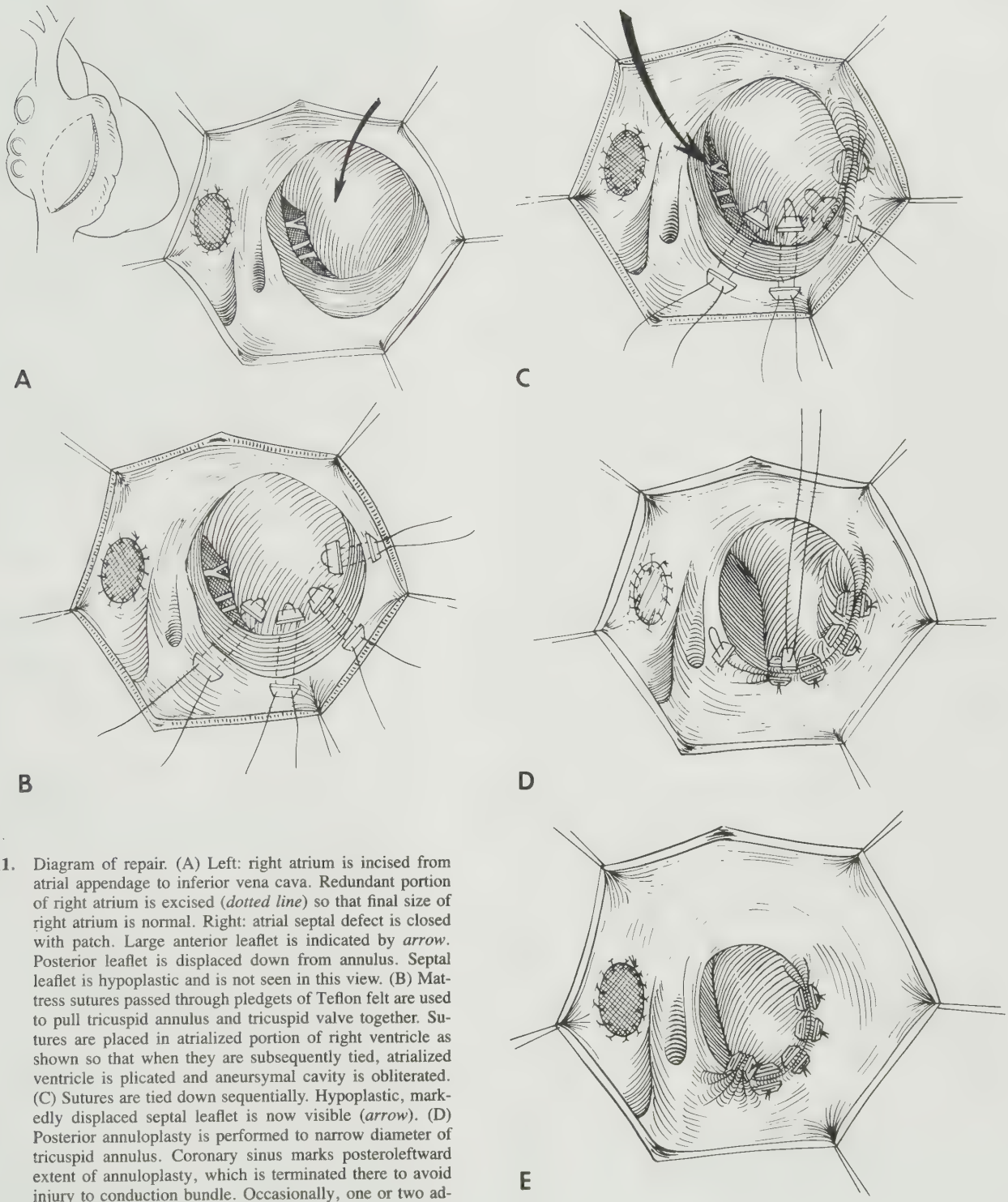

Fig. 68–11. Diagram of repair. (A) Left: right atrium is incised from atrial appendage to inferior vena cava. Redundant portion of right atrium is excised (*dotted line*) so that final size of right atrium is normal. Right: atrial septal defect is closed with patch. Large anterior leaflet is indicated by *arrow*. Posterior leaflet is displaced down from annulus. Septal leaflet is hypoplastic and is not seen in this view. (B) Mattress sutures passed through pledgets of Teflon felt are used to pull tricuspid annulus and tricuspid valve together. Sutures are placed in atrialized portion of right ventricle as shown so that when they are subsequently tied, atrialized ventricle is plicated and aneursymal cavity is obliterated. (C) Sutures are tied down sequentially. Hypoplastic, markedly displaced septal leaflet is now visible (*arrow*). (D) Posterior annuloplasty is performed to narrow diameter of tricuspid annulus. Coronary sinus marks posteroleftward extent of annuloplasty, which is terminated there to avoid injury to conduction bundle. Occasionally, one or two additional mattress sutures are required to obliterate posterior aspect of annuloplasty repair in order to render valve totally competent. Tricuspid annulus at this time will admit two or more fingers. (E) Completed repair which allows anterior leaflet to function as a monocusp valve. (Modified from Danielson, G.K., Maloney, J.D., and Devloo, R.A.E.: Surgical repair of Ebstein's anomaly. Mayo Clin. Proc., *54*:185, 1979. By permission of Mayo Foundation.)

in the infant with severe congestive heart failure or cyanosis are less clear and must be individualized after careful deliberation.

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CHAPTER 69

Anomalous Pulmonary Venous Connections; Pulmonary Vein Stenosis; Atresia of the Common Pulmonary Vein

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Charles E Mullins

This chapter deals with abnormalities in the pulmonary venous circulation including anomalous pulmonary venous connections (partial and total), pulmonary vein stenosis, and atresia of the common pulmonary vein. Cor triatriatum, an abnormality thought by many to have a similar embryologic origin, will not be discussed here but will be presented in Chapter 77.

ANOMALOUS PULMONARY VENOUS CONNECTIONS

Definition of Terms

We will use the term *anomalous venous connections* as proposed by Edwards[1] rather than *drainage* or *return* in order to define more clearly the anatomy of this complex of cardiac defects. Anomalous pulmonary venous drainage may occur without anomalous connection; for example, a large atrial septal defect or common atrium in which pulmonary venous blood from the right lung, although connected normally, drains directly into the right atrium. Anomalous connection, on the other hand, when defined as at least one pulmonary vein connected to the right atrium either directly or through a venous tributary, always denotes anomalous drainage. Partial anomalous pulmonary venous connection (PAPVC) occurs when one or more but not all pulmonary veins connect anomalously to the right atrium. PAPVC, which is often found in association with an atrial septal defect, usually demonstrates hemodynamic findings of increased pulmonary blood flow.

When all pulmonary veins connect anomalously to the systemic venous circulation, total anomalous pulmonary venous connection (TAPVC) is defined. TAPVC is associated with total mixing of pulmonary and systemic venous blood at the level of the right atrium; it may demonstrate increased or decreased pulmonary blood flow. If there is increased pulmonary blood flow, the patient may not have visible cyanosis; if there is reduced pulmonary blood flow (usually found with obstruction to venous return), the infant may be cyanotic. In addition, TAPVC is always associated with an interatrial communication.

Historical Perspective

The first reported case of anomalous pulmonary venous connection was by Winslow in 1739, when he described a single vein from the right upper lobe draining into the superior vena cava.[2] Sporadic case reports continued throughout the early nineteenth century, most of which emanated from the European continent. In 1868, Friedlowsky[2] reported the first case of TAPVC without associated cardiac defects in an 18-day-old infant with drainage to the left innominate vein. Brody,[2] in a classic paper published in 1942, compiled 100 previously reported cases and added 2 of his own. This paper was the first in-depth review of the subject and improved understanding of the anatomic variants and basic pathophysiology of this complex of cardiac defects. That report discussed the concepts that PAPVC usually is associated with a normal or near-normal life span, and that TAPVC is a disease process that most often leads to death in the first year of life unless a large interatrial communication exists. These observations were confirmed and enlarged by a number of investigators.[4–10] The work of Neill[11] in 1956 and Darling et al.[12] in 1957 led to a classification system based on embryologic and anatomic considerations, respectively.

The antemortem diagnosis of partial anomalous pulmonary ve-

nous connection using cardiac catheterization and angiocardiography was first reported by Dotter et al.[13] in 1949. Shortly thereafter, Friedlich and associates[14] reported their results of catheterization in 18 patients with anomalies in pulmonary venous connection; 2 of these had total anomalous pulmonary venous connection. With accurate and complete catheterization and angiocardiographic diagnoses, attempts at surgical correction ensued. In 1951, Muller[15] reported partial correction of TAPVC with the use of a closed anastomosis between the left atrial appendage and the left upper pulmonary vein. Burroughs and Kirklin,[16] using the atrial well technique, and Lewis et al.[17] using moderate hypothermia and inflow occlusion, reported successful surgical repair of TAPVC in 1956. In that same year, Cooley and Ochsner[18] performed the first successful correction of TAPVC using cardiopulmonary bypass. In the 30 years since the first report of successful surgical treatment of these abnormalities, advances in the understanding of the pathophysiology of TAPVC as well as improvements in diagnostic and operative techniques have led to a dramatic decrease in morbidity and mortality associated with these defects.

Embryology

A review of the embryologic development of the systemic and pulmonary venous systems will illuminate the nature of the many and varied abnormalities observed in patients with anomalies of pulmonary venous connection.

In the developing embryo, the primitive foregut gives rise to the lungs, larynx, and tracheo–bronchial tree. The primordial lung buds share a common vascular plexus (splanchnic plexus) with other derivatives of the foregut and, early on, drain through the paired common cardinal and umbilicovitelline veins (Fig. 69–1A). As development proceeds, this splanchnic plexus differentiates into the primitive pulmonary vascular bed and thus will drain pulmonary venous blood. This pulmonary vascular bed, however, remains in communication with the cardinal and umbilicovitelline system of veins until somewhat later in development. The right common cardinal system will later differentiate into the right horn of the sinus venosus, which will in turn give rise to the right superior vena cava and azygous vein. The left common cardinal system will become the left horn of the sinus venosus and, through further differentiation, give rise to the left superior vena cava and coronary sinus. The umbilicovitelline system will become the inferior vena cava, ductus venosus, and portal vein. At this stage of development (3 to 5 mm embryo, 25 to 27 days' gestation), there is no direct communication to the developing heart (see Fig. 69–1A).

Auer[19] and Neill[11] have contributed greatly to the understanding of early development of the pulmonary venous circulation. At 27 to 29 days' gestation, the primitive pulmonary vein can be seen as a small endothelial outgrowth from the posterior superior wall of the primordial left atrium. This vein lies directly to the left of the developing septum primum and also to the left and inferior to the left valve of the sinus venosus. At 28 to 30 days' gestation, the pulmonary vein has engaged the pulmonary portion of the splanchnic plexus, and thus begins to drain blood from this region (Fig. 69–1B). The pulmonary portion of the splanchnic plexus begins to lose connections with the cardinal and umbilicovitelline systems at this time. With further development, this separation becomes complete except for very small anastomoses between the

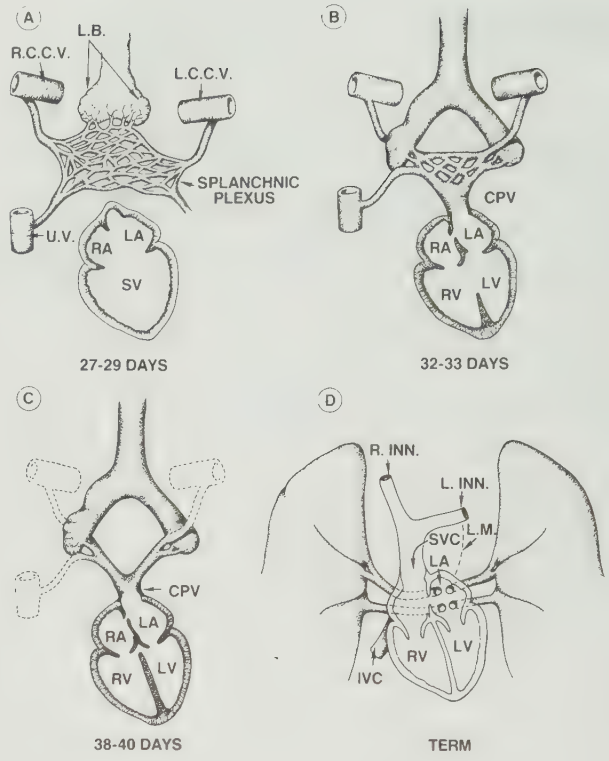

Fig. 69–1. Development of the pulmonary venous system. (A) At 27 to 29 days gestation, the primordial lung buds share a common vascular plexus (splanchnic plexus) with other derivatives of the foregut and drain through the paired right and left common cardinal (R.C.C.V., L.C.C.V.) and umbilicovitelline (U.V.) veins. A small endothelial outgrowth arises from the left atrium directly to the left of the septum primum and grows into the splanchnic plexus.' (B) This common pulmonary vein (C.P.V.) allows blood to drain directly to the heart, although at this stage it may still drain indirectly through the primitive venous connections. (C) Once the direct left atrial connection is established, the primitive pulmonary venous connections disappear. (D) Further differential growth of the left atrium leads to incorporation of individual pulmonary veins into the left atrium, usually with two veins from each lung connecting separately. CPV, common pulmonary vein; IVC, inferior vena cava; LA, left atrium; L.C.C.V., left common cardinal vein; L.B., lung buds; L.Inn., left innominate vein; L.M., Ligament of Marshall; L.A., left atrium; L.V., left ventricle; R.C.C.V., right common cardinal vein; R.Inn., right innominate vein; R.A., right atrium; R.V., right ventricle; S.V., single ventricle; S.V.C., superior vena cava. (Adapted from Lucas, R.V., et al.: Congenital causes of pulmonary venous obstruction. Pediatr. Clin. North Am., *10*:781, 1963.)

pulmonary and bronchial veins (bronchopulmonary veins). Tributaries to the pulmonary vein coalesce to form a well-defined common chamber, which is incorporated progressively into the posterior wall of the primitive left atrium (Fig. 69–1C). The final result is a left atrial chamber whose volume is made up of approximately equal parts of common pulmonary vein and primitive left atrium; the primitive left atrium includes the left atrial appendage.[20,21] This concept is important in understanding later anatomic and pathophysiologic findings in patients with TAPVC.

Complete incorporation of the common pulmonary vein into the left atrium usually results in two right and two left pulmonary veins entering through separate orifices (Fig. 69–1D). Variation

in number of pulmonary veins draining into the left atrium is common. Healy[7] found the most common variant (occurring in 24% of autopsy specimens) to be the presence of a single pulmonary vein draining either the right or left lung. The next most frequent variation occcurred in 2% of specimens and consisted of an extra pulmonary vein entering the left atrium, most commonly from the right lung. On rare occasions, a fourth or fifth vein may drain the right lung.[7] These variations in anatomy are of no hemodynamic consequence, although knowledge of their existence may be important in surgical procedures involving the left atrium.

The anatomic variations that occur in anomalous pulmonary venous connection can be readily explained by alterations in the normal sequence of embryologic events.[11,12] Thus, anomalous pulmonary venous connection directly to the right atrium occurs when the primum septum grows abnormally far to the left, leading to incorporation of the common pulmonary vein to the right. If the common pulmonary vein fails to develop, or if development proceeds early but then later the communication between the left atrium and the pulmonary vein is disrupted, primitive channels between the pulmonary plexus and the cardinal and umbilicovitelline system will persist. Drainage to the left common cardinal system results in anomalous pulmonary venous connection to either the coronary sinus or left innominate vein. Drainage to the right common cardinal system leads to pulmonary venous connection to the superior vena cava and/or azygous vein. Finally, drainage to the umbilicovitelline system results in pulmonary venous connection to the portal vein, ductus venosus, or inferior vena cava.

The timing and degree of obliteration of the common pulmonary vein/left atrial connection determine the nature of the abnormalities apparent after birth.[23] Early atresia of the common pulmonary vein, while primitive pulmonary–systemic venous connections are still present, will lead to TAPVC (Fig. 69–2B[1]). If only the right or left portion of the common pulmonary vein becomes atretic, persistence of the primitive pulmonary venous–systemic venous connection on that side would lead to PAPVC (Fig. 69–2A[1]). If atresia of the common pulmonary vein occurs after complete obliteration of the primitive pulmonary venous–systemic venous connections, then atresia of the common pulmonary vein would result. This defect is rare and is nearly always fatal because the pulmonary veins empty into a blind chamber, the only egress of pulmonary venous blood occurring through very small bronchopulmonary anastomoses.[24] This anomaly will be discussed further in the final section of this chapter. Incomplete incorporation of the common pulmonary vein into the left atrium would, according to this schema, lead to the syndrome of stenosis of the common pulmonary vein, or cor triatriatum. That this anomaly may be a spectrum of abnormalities of common pulmonary vein development is illustrated by the rare occurrence of both cor triatriatum and anomalous pulmonary venous connection in the same patient. (Cor triatriatum will be discussed in depth in Chapter 77.) Finally, abnormal incorporation of the common pulmonary vein into the left atrium may lead to abnormal numbers of pulmonary veins as described previously. Inadequate absorption of the common pulmonary vein would result in fewer than the normal number of veins, and exaggerated absorption would lead to increased numbers of pulmonary veins.

Although some authors consider stenosis of the individual pulmonary veins to represent an abnormality of common pulmonary vein incorporation,[24] this remains controversial. This subject, also, will be discussed later in this chapter.

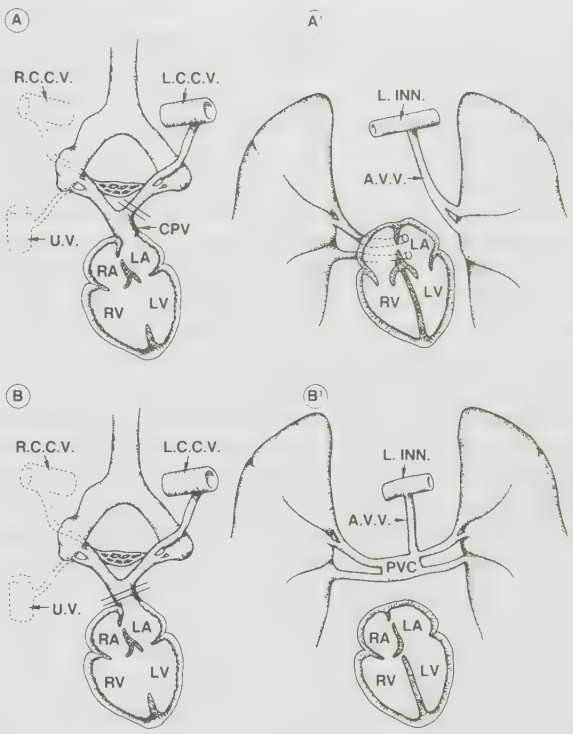

Fig. 69–2. Embryology of anomalous pulmonary venous connections. (A) The primitive left atrium (LA) is connected to the pulmonary venous plexus by the common pulmonary vein (CPV). Partial interruption of this connection early in gestation leads to persistence of ipsilateral systemic venous channels, which results in partial anomalous pulmonary venous connection (A[1]). (B) Complete interruption of the common pulmonary vein results in total anomalous pulmonary venous connection (B[1]). A.V.V., anomalous vertical vein; PVC, pulmonary venous confluence; other abbreviations as in Figure 69–1. (Adapted by Edwards, J.E.: Pathologic and developmental considerations in anomalous pulmonary venous connection. Mayo Clin. Proc., *28*:441, 1953.)

PARTIAL ANOMALOUS PULMONARY VENOUS CONNECTION

Partial anomalous pulmonary venous connection (PAPVC) occurs when one or more, but not all, of the pulmonary veins drain into the right atrium directly or indirectly by venous connections. Adachi[25] and Hughes and Rumore[26] have reported PAPVC in 0.7% of autopsy specimens. Healey[7] found 1 case in 251 autopsies and, combining this incidence (0.4%) with those of the previous two studies, determined an overall incidence of 0.6%. The relatively high incidence of this defect observed in autopsy specimens suggests that it is more common than clinical series imply. In fact, many cases of PAPVC do not produce symptoms and are thus not diagnosed during life.

Although PAPVC is associated with other types of cardiopulmonary malformations, there are no known risk factors for the development of this anomaly. In addition, prenatal teratogens (drugs, infections) have not been implicated as causal agents. Risk

of recurrence of the isolated lesion in subsequent siblings of a patient are unknown. Since clinically apparent anomalies in pulmonary venous connection usually occur in patients with associated cardiac defects, the recurrence risks in these families likely parallel those of the associated defect.[27]

Anatomy

Because of the multiplicity of connections between the primitive pulmonary vascular bed and the systemic venous circulation, PAPVC represents a wide spectrum of anatomic variants. Blake et al.[28] observed 27 different variations in 113 selected cases of anomalous venous connection. According to Brody's[2] data, which was confirmed later by Healey[7] and Hickie,[29] the most common types of PAPVC are (in order of decreasing frequency) right pulmonary veins to right superior vena cava, right pulmonary veins to right atrium, right pulmonary veins to inferior vena cava, and left pulmonary veins to the left innominate vein. Connection from the right lung anomalously occurs about twice as frequently as the left. Partial connection to the coronary sinus and azygous vein is less frequent. The more common types of partial anomalous pulmonary venous connection are shown schematically in Figure 69–3A–C.

PAPVC may occur 1) as an isolated defect; 2) in association with other cardiac defects; or 3) in the setting of cardiac malposition and bronchovascular anomalies (scimitar syndrome). PAPVC as an isolated defect is uncommon in patients referred for cardiac evaluation; only 100 cases have been reported as of 1983.[30] The majority of patients who develop signs and symptoms related to this defect usually have two or more anomalously connecting veins; a single anomalous vein is rarely clinically important.

Usually, PAPVC is found in association with other cardiac defects, most commonly an ASD of the secundum or sinus venosus type.[29] Approximately 10% of patients with a proven ASD have PAPVC.[31] Less frequently, partial anomalous pulmonary venous connection has been associated with dextrocardia, azygous continuation of the inferior vena cava, congenital mitral stenosis or atresia, double outlet right ventricle, ventricular septal defect, tetralogy of Fallot, pulmonic stenosis, coarctation of the aorta, patent ductus arteriosus, aortic stenosis, and hypoplasia of the aorta.[31]

PAPVC from the right lung to the inferior vena cava occurs in the Scimitar syndrome. This complex of anomalies, which includes pulmonary hypoplasia or sequestration, diaphragmatic abnormalities, and anomalous systemic arterial supply to the right lung, usually is associated with an intact atrial septum. Associated cardiac defects are seen in approximately one-fourth of patients and include VSD, PDA, coarctation of the aorta, and tetralogy of Fallot. This complex of anomalies represents a more primitive abnormality of development of the right lung buds rather than an isolated abnormality of the primordial pulmonary venous system.[32] A detailed description of the more common anatomic variants follows.

Right Pulmonary Veins to Superior Vena Cava and/or Right Atrium

This abnormality in PAPVC is the most common variant, occurring in 74% of patients studied by Brody.[2] In PAPVC to the superior vena cava (SVC), the right upper and middle lobe veins drain separately into the SVC between the entry of the azygous vein and the right atrial/superior vena caval junction (see Fig. 69–3A). Infrequently, the right upper lobe drains through two or three smaller veins that enter separately into the superior vena cava. The right lower lobe pulmonary vein most often enters the left atrium normally; however, this too may drain anomalously to the right atrium. In the majority of cases, PAPVC to the SVC is associated with an atrial septal defect (ASD) of the sinus venosus type. This defect is located in the superior/posterior portion of the atrial septum near the entrance of the SVC; occasionally, the SVC orifice may override this defect, directing a portion of superior caval flow into the left atrium. Dilatation of the lower SVC occurs in response to increased blood flow through this region.

In most cases of anomalous connection directly to the right

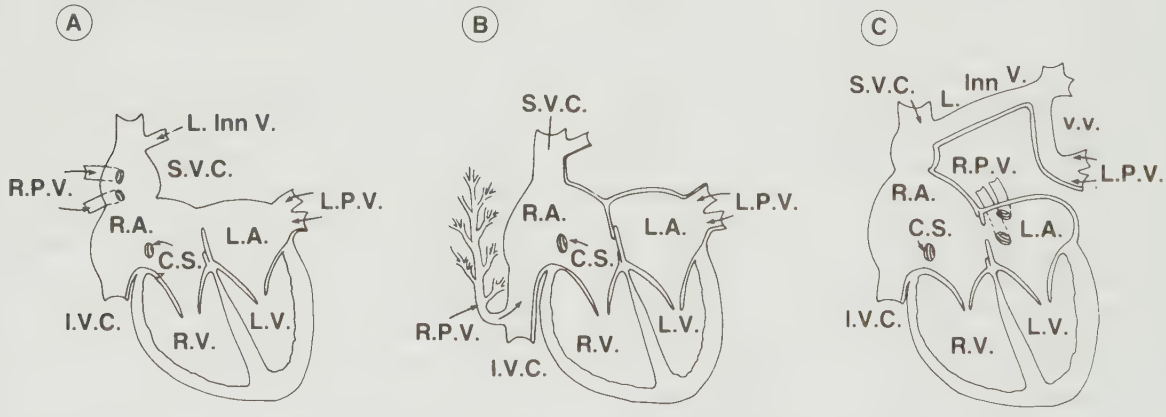

Fig. 69–3. Common types of partial anomalous pulmonary venous connection. (A) Right pulmonary veins (R.P.V.) connecting to superior vena cava (S.V.C.) or high right atrium (R.A.). This anomalous connection is often associated with a sinus venosus atrial septal defect. (B) Anomalous connection from the right lung by a single pulmonary vein to the inferior vena cava (I.V.C.) is usual in the Scimitar syndrome (pulmonary parenchymal abnormalities with anomalous systemic arterial supply). (C) Anomalous connection of one or more left pulmonary veins (L.P.V.) to the left innominate vein (L.Inn.V.) by an ascending vertical vein (V.V.). C.S., coronary sinus; other abbreviations as in Figure 69–2. (Adapted from Lucas, R.V.: Anomalous Venous Connections, Pulmonary and Systemic. *In* Heart Disease in Infants, Children, and Adolescents. Edited by F.H. Adams and G.C. Emmanouilides. 3rd Ed. Baltimore, Williams & Wilkins, 1983.)

atrium, the entire right lung drains anomalously by two or three separate veins. These veins enter at the posterior interatrial groove just to the right of the atrial septum. A sinus venosus type atrial septal defect is most often present, although secundum and primum defects may occur. Rarely, the atrial septum is intact.

Right Pulmonary Veins to Inferior Vena Cava

In this circumstance, most or all of the veins draining the right lung form a confluence and enter the inferior vena cava as a single trunk (see Fig. 69–3B). This trunk forms in the region of the hilum and passes inferiorly and to the left along the greater fissure to enter the inferior vena cava just above or below the diaphragm.[33] Rarely, the trunk may terminate blindly within the diaphragm. Infrequently, only the right middle or right lower lobe pulmonary vein may connect anomalously.

Left Pulmonary Veins to Left Innominate Vein/Coronary Sinus

Anomalous connection from the left lung usually occurs to remnants of the left cardinal system, including the left innominate vein and coronary sinus. Most commonly, the left upper lobe drains to the innominate vein by a single trunk, with the left lower lobe draining normally to the left atrium (see Fig. 69–3C). The nomenclature of the ''anomalous trunk'' that connects the pulmonary veins from the left lung to left innominate vein is debated. Some authors refer to this as a persistent left superior vena cava,[1] which denotes a direct connection to the heart through the coronary sinus. Others refer to it simply as an anomalous vertical vein, which we prefer.[34]

One or more of the left pulmonary veins, usually draining from the left lower lobe, may connect to the coronary sinus. This isolated abnormality is uncommon and was found in only one case in the extensive series of Brody[2] and in no patient in the study of Hickie.[29] Less frequently, anomalous veins from the left lung may drain into the right atrium, inferior vena cava, right superior vena cava, or left subclavian vein. Rarely, anomalous veins from the right lung connect across the midline to the coronary sinus or innominate vein, and one or more veins from the left lung connect to the SVC or right atrium.

Physiology and Hemodynamics

The basic hemodynamic alteration that occurs in PAPVC is a pre-tricuspid left to right shunt, in which fully oxygenated blood is recirculated through the lungs through the right atrium, right ventricle, and pulmonary artery. The increased pulmonary blood flow leads to enlargement of the right atrium, enlargement and hypertrophy of the right ventricle, and dilatation of the pulmonary artery. The left heart chambers are not affected, and systemic cardiac output is normal.

Isolated PAPVC

In the case of PAPVC without associated cardiac defects, the magnitude of the left to right shunt depends on: 1) the number of anomalously draining veins as a percentage of the total pulmonary venous return; 2) the pulmonary segments or lobes from which the anomalous veins originate; and 3) the relative resistances of the normally and abnormally drained pulmonary vascular beds and the compliance of the receiving chambers into which the respective veins empty.[34]

Brody[2] first suggested that hemodynamic abnormalities will not be clinically apparent in patients with isolated PAPVC until 50% or more of the pulmonary blood flow drains anomalously. He based these observations on the finding that 25 of 27 patients (93%) with less than 50% anomalous pulmonary venous connection survived to adulthood, whereas more than half of patients with anomalous pulmonary venous connection draining greater than 50% of the total pulmonary blood flow died in childhood. Hughes[26] studied two patients dying of rheumatic valve disease in middle age, both of whom had PAPVC draining a single lobe. Neither patient had dilatation or hypertrophy of the right heart despite the observation that 25% of total pulmonary blood flow was being shunted left to right. These initial observations have been supported by subsequent studies, suggesting that one lobe connecting anomalously is associated with minimal cardiac pathology and (usually) a normal life span.

The second factor determining the magnitude of left-to-right shunt in PAPVC is the lobe or lobes involved in the anomalous connection. At rest in the upright position, blood flow in the lungs is distributed preferentially to the middle and lower lobes, with minimal flow to the apices of both lungs. Isolated PAPVC from one or the other upper lobes would result in less left-to-right shunt than veins connecting anomalously from the middle to lower lobes. On assuming the supine position or during exercise, pulmonary blood flow is redistributed to the upper lobes, thus increasing the left-to-right shunt. These factors may explain the variation observed in calculated pulmonary to systemic flow ratio in patients undergoing serial hemodynamic evaluation.

The last factor that plays a role in the distribution of pulmonary venous return in PAPVC is regional pulmonary vascular resistance and the downstream compliance to pulmonary venous return. Patients with an abnormal pulmonary vascular bed (such as is seen in some patients with scimitar syndrome) may have elevated pulmonary arteriolar resistance in the lung that drains anomalously. Pulmonary blood flow will proceed preferentially through the normal pulmonary venous pathways through the left lung and tend to reduce the left-to-right shunt. This phenomenon is observed in unilateral pulmonary vein stenosis in which pulmonary arterial flow is shunted to the lung with unobstructed venous return. If the pulmonary arteriolar resistance is equal throughout both lungs, and if the anomalous pulmonary vein connects unobstructed to the right atrium, then pulmonary blood flow will proceed preferentially through this anomalous connection if the right atrial pressure is significantly less than left atrial pressure.[35] When left atrial pressure is elevated abnormally (mitral stenosis), pulmonary blood flow through the anomalous connection will be exaggerated. All of these factors must be taken into account when determining the degree of hemodynamic alteration and, in the final analysis, the indication for surgical intervention in patients with isolated PAPVC.

Although rare, pulmonary hypertension and documented pulmonary vascular disease have been reported in at least 5 patients with isolated PAPVC.[29,35,36] This association most likely represents a coincidental occurrence; a cause and effect relationship is highly unlikely.

PAPVC with Associated Cardiac Defects

PAPVC with an associated small atrial septal defect resembles closely the hemodynamic findings as just described. When the

atrial defect is of considerable size, the additional left-to-right shunt increases the burden on the right heart and pulmonary circulation. Pulmonary blood flow/systemic blood flow ratios of greater than 3:1 are found commonly and result from both a left-to-right shunt through the anomalous venous connection and the left-to-right shunt at the atrial level. A small right-to-left shunt may be detectable by dye curves or contrast echocardiography in certain cases. This usually occurs in the setting of anomalous pulmonary venous connection to the superior vena cava in association with a sinus venosus type atrial septal defect and overriding of the SVC. Systemic arterial desaturation rarely is observed unless intrapulmonary ventilation/perfusion abnormalities are present.

Elevation of calculated pulmonary vascular resistance and pulmonary artery pressure in the presence of PAPVC with only an atrial septal defect has been reported.[29] The incidence probably is similar to that found in an isolated atrial septal defect. Whether the increase in pulmonary blood flow contributed by the additional anomalous pulmonary venous connection leads to earlier pulmonary vascular disease in a susceptible individual is not known.

The physiology in patients with associated intracardiac defects other than ASD most often is determined by the severity of those associated defects. Alpert[35] performed catheterizations on seven patients with PAPVC and mitral stenosis and observed hemodynamic findings consistent with those found in patients with pure mitral stenosis alone. In a number of these patients, pulmonary blood flow to the anomalously draining lung was significantly greater than expected, suggesting that pulmonary venous return followed the path of least resistance and was acting as a compensatory mechanism to decrease the pressure load in the normally connecting pulmonary venous circuit.

Clinical Features

History and Physical Examination

Most patients with PAPVC with or without an interatrial communication do not exhibit symptoms in early life. These patients are often referred with a cardiac murmur or an abnormal chest roentgenogram. When symptoms are elicited at this age, the most common complaint is mild exercise intolerance. Progressive symptoms, if they appear, usually begin in the mid-thirties or early forties. These consist of dyspnea, recurrent bronchitis, hemoptysis, chest pain, and palpitations associated with supraventricular arrhythmias. When overt cardiac failure occurs, its onset is usually rapid.[29] The natural history and clinical findings parallel closely those observed in the symptomatic patient with an ASD.

Respiratory symptoms of dyspnea on exertion and/or recurrent pneumonia may be observed in patients with scimitar syndrome because of pulmonary parenchymal abnormalities. Patients with PAPVC and associated cardiac defects other than an atrial septal defect usually have symptoms and signs related to the associated defect.

Physical examination in patients with isolated PAPVC may be entirely normal if only a single lobe connects anomalously. When multiple lobes are involved, or when there is an associated ASD, the findings are typical of an uncomplicated ASD. There is an increased right ventricular impulse, a basal low-pitched systolic ejection murmur, and wide, fixed splitting of the second heart sound. A diastolic murmur over the tricuspid valve may be detected. Rarely, there may be a low-frequency continuous murmur heard over the base, representing flow through an anomalous venous channel. In older symptomatic patients, cyanosis is found in 50% and is due to both pulmonary hypertension with right-to-left atrial level shunt and also pulmonary venous desaturation.[29] Overt signs of right heart failure (hepatomegaly, jugular venous distention, ascites) may be observed in the older, severely affected patient.

Electrocardiogram

The electrocardiogram most often reveals right ventricular hypertrophy of the volume type with a rR′ pattern or a rSR′ pattern in the right precordial leads. In the older patient with pulmonary hypertension, right atrial enlargement and severe right ventricular hypertrophy are seen. The electrocardiogram may be normal in patients without associated cardiac defects.

Atrial arrhythmias, including atrial flutter and fibrillation, may occur in the third and fourth decade and usually are associated with an atrial septal defect or mitral stenosis. The development of these arrhythmias relates to the magnitude of left-to-right shunt and subsequent atrial dilatation, although some studies have suggested a correlation with the onset of pulmonary hypertension.[37] Kyger[38] found atrial arrhythmias in 14% of patients undergoing operation for sinus venosus atrial septal defect and PAPVC. The mean age of operation in these patients was 14 years. The incidence of atrial arrhythmias increases with age and was found in 55% of patients older than 60 years undergoing surgery for an isolated ASD or an ASD associated with PAPVC.[39]

Radiographic Features

The chest roentgenogram often shows, in the presence of an atrial septal defect, evidence of right atrial and right ventricular enlargement in addition to increased pulmonary vascularity. In the absence of an atrial defect or other associated anomalies, the chest roentgenogram is usually normal.

Specific findings related to the insertion or drainage of the anomalous pulmonary venous connection have been well described. When veins from the left lung enter a confluence and drain to the left innominate vein, the abnormal vessel may be seen as a widened superior mediastinum on the left. This structure may be seen to pulsate under fluoroscopy. Increased blood flow in the left innominate vein and superior vena cava may cause enlargement of these structures, thus forming the classic figure-eight pattern first reported by Snellen and Albers.[40] In cases in which anomalous right pulmonary veins enter the superior vena cava, a widened superior vena cava/right atrial segment and a prominent vascular structure extending into the right upper lobe may be visible.

The most widely described radiographic finding in PAPVC occurs when the right lung drains anomalously by a single trunk to the inferior vena cava at the level of the diaphragm, the anomalous trunk resembling a curved scimitar sword. This classic finding, when associated with malposition of the heart and hypoplasia of the right lung with aberrant systemic arterial supply, was termed scimitar syndrome by Neill[32] in 1960 (Fig. 69–4).

Echocardiography

PAPVC with or without an atrial septal defect has M-mode echocardiographic findings similar to those reported for atrial septal defects alone.[41] There is mild to moderate dilatation of the right ventricle and usually paradoxical interventricular septal motion.

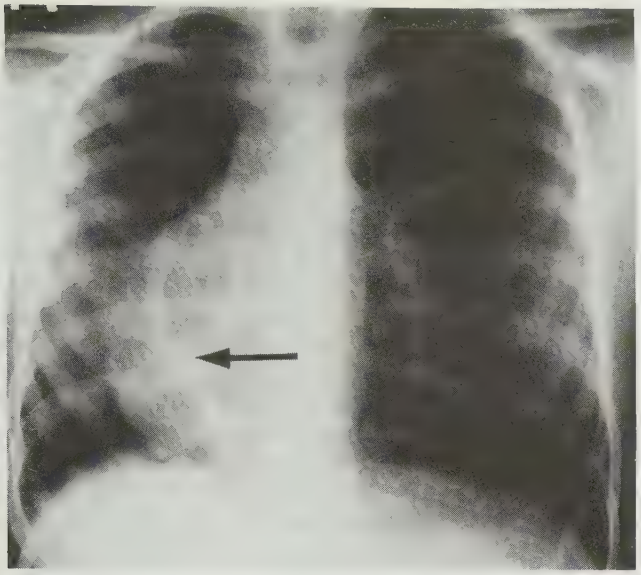

Fig. 69–4. Scimitar syndrome. Chest radiograph in a patient with dextrocardia and partial anomalous pulmonary venous connection from the right lung to the inferior vena cava. Arrow points to the anomalous (Scimitar) vein. (Courtesy of Teresa Stacy, M.D.)

High-resolution two-dimensional ultrasound imaging of intracardiac structures and intrathoracic arteries and veins has supplanted M-mode echocardiography as the prime noninvasive diagnostic procedure of choice in patients with suspected abnormalities of pulmonary venous connection. The addition of pulsed and continuous-wave Doppler echocardiography has expanded the ability to assess abnormalities in structure as well as function in these patients.

In infants and young children, the interatrial septum can usually be well visualized using two-dimensional imaging from the subcostal four-chamber view. Atrial defects of the sinus venosus type, which occur more commonly with PAPVC, may be difficult to image in this routine tomographic plane.[42] Visualization of this defect may be enhanced by clockwise rotation of the imaging plane from the subcostal four-chamber view 90 degrees to a subcostal sagittal plane. Using this technique, the posterior/superior atrial septum is interrogated easily. If a defect of the sinus venosus type is detected, then a diligent search for anomalous pulmonary venous connection should be performed.

Direct visualization of anomalous pulmonary venous connections requires a knowledge of anatomy as well as a high index of suspicion. When the clinical diagnosis of PAPVC is suspected or in the presence of a sinus venosus ASD, careful scanning in the suprasternal and subcostal planes should be performed to detect the absence of one or more normally connecting pulmonary veins. If all four veins are not visualized, imaging the left innominate vein to its birfurcation should be performed. Partial anomalous pulmonary venous connection from the left lung may be visualized as a vascular structure entering the inferior aspect of the left innominate vein. Doppler interrogation of this structure will reveal a venous flow pattern in a cranial direction and thus establish the diagnosis. Although somewhat more difficult to observe, the anomalous right pulmonary vein connecting to the superior vena cava also should be apparent from the suprasternal notch with scanning in the suprasternal short axis or sagittal plane. Subcostal short and long axis scans at the level of the inferior vena cava/right atrial junction should be performed in all patients in whom the diagnosis of Scimitar syndrome is being considered. Finally, scanning of the posterior left atrioventricular groove will reveal an enlarged coronary sinus in patients with partial anomalous connection to this location. Using a step-by-step sequential approach, the more common types of PAPVC will be readily detected or at least highly suspected. One must remember, however, that structures coursing outside the mediastinum in the lung parenchyma cannot be visualized due to acoustic interference from air-filled lung. Because of these limiting factors, many patients will require further diagnostic studies in order to delineate precisely the complete anatomy of the suspected lesion.

Cardiac Catheterization and Angiography

Cardiac catheterization with selective angiography remains the definitive diagnostic procedure in most patients with suspected PAPVC with or without associated cardiac defects. Dotter and associates[13] in 1949 first reported the catheterization and angiographic findings in 2 patients with PAPVC to the inferior vena cava. The first large series was by Friedlich[14] in which he reported findings on 16 patients with PAPVC. Refinements in catheterization technique and the introduction of axial cineangiography further enhanced the ability to define both anatomic and hemodynamic alterations in this lesion.

From the femoral vein approach, the anomalous vein may be entered directly during catheter probing. If the catheter passes directly into a pulmonary vein from the right lateral border of the right atrium or low superior vena cava, the diagnosis of anomalous pulmonary venous connection from the right lung to this region should be suspected. The catheter course in this circumstance may be confused with a normal course in which the catheter crosses a patent foramen ovale or an ASD and enters the normally connecting right upper pulmonary vein. One may resolve this question by 1) observing an initial posterior course of the catheter in the left anterior oblique view or 2) slow withdrawal from the vein observing a quick rightward slip of the catheter tip some distance from the right atrial border.[31]

Manipulation of the catheter into the left innominate vein should always be performed in suspected cases with oximetry sampling distally and at the innominate vein/SVC junction. Probing in the left innominate vein at the mediastinal border is done to detect an anomalously connecting pulmonary vein from the left lung. Oximetry sampling should be performed at multiple sites during a pull back from the high superior vena cava into the body of the right atrium to discern a significant step up (7 to 10%) in oxygen saturation. Although an isolated sinus venosus type atrial septal defect may imply an anomalous pulmonary venous connection at the SVC/right atrial junction, selective axial cineangiography should resolve this question. In cases of suspected Scimitar syndrome, the inferior vena cava should be investigated thoroughly. Oximetry sampling may be confusing in this region because of the higher oxygen saturations that normally occur in the IVC due to the high renal vein oxygen content.

Intracardiac pressures are most often normal in patients with PAPVC when less than 50% of the pulmonary veins connect anomalously. The exceptions to this include patients older than 40 years of age with an associated ASD,[29,38,39] those with concomitant

mitral stenosis,[43] and those with the scimitar syndrome.[33,44] In these circumstances, elevation of right atrial, right ventricular, and pulmonary artery pressures may be observed.

Cineangiography

Selective cineangiography should be performed in all cases of suspected PAPVC in patients undergoing cardiac catheterization. The levophase of a selective right or left pulmonary artery angiogram may reveal the lobe or lobes that are connected anomalously. Further delineation by lobar or segmental injection may be required. If the anomalous vein can be entered directly, injection of contrast material into the anomalous connection with angulated cineangiography is helpful to define both the connection and drainage in cases of PAPVC (Fig. 69–5).

Indicator dilution studies[45] and contrast echocardiography[46] may be useful adjuncts during catheterization to delineate some forms of PAPVC. We have not used these methods extensively but think they may have a place in certain diagnostic situations.

Other Diagnostic Modalities

Newer imaging modalities have been developed recently that may have application in both anatomic diagnosis or hemodynamic assessment of these cardiac defects. These include radionuclide angiocardiography and magnetic resonance imaging (MRI).

The application of radionuclide studies in congenital heart disease has been discussed recently in depth by Hurwitz and Treves.[47] First-pass angiocardiography provides an anatomic delineation of intracardiac and extracardiac vascular structures and also can be used to quantitate shunting between the pulmonary and systemic circulations. The anatomic detail provided by radionuclide studies is inferior to those of high-resolution echocardiography and selective angiography, however, and should be used in conjunction with these modalities in the preoperative assessment. Serial studies using first-pass radionuclide angiocardiography to predict pulmonary to systemic blood flow ratios (Qp/Qs) would appear helpful in following patients who are borderline surgical candidates.

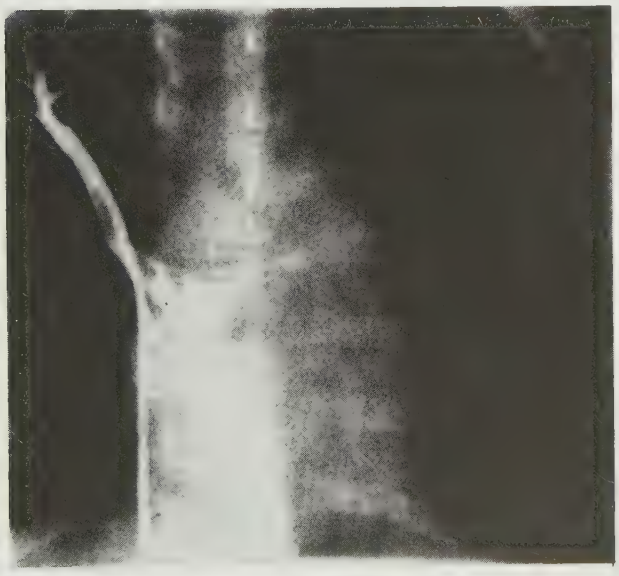

Fig. 69–5. Angiography in PAPVC. Direct contrast injection into the right upper pulmonary vein demonstrates anomalous connection to the high right atrium.

Cardiac-gated magnetic resonance imaging (MRI) is a noninvasive technique that demonstrates in fine detail both intracardiac and intrathoracic anatomy without the use of ionizing radiation. The utility of this methodology to supplant more conventional imaging techniques, however, is yet to be demonstrated. Further studies using MRI are forthcoming, and will likely complement the well-established diagnostic techniques.

Natural History of PAPVC

In patients with isolated PAPVC without associated defects, the prognosis depends on the number of pulmonary veins draining anomalously. Studies based on autopsy material[2,26] indicate that patients with a single pulmonary vein connected anomalously and an intact atrial septum rarely have symptoms and have a normal life expectancy. Patients in whom more than 50% of pulmonary veins drain anomalously or who have an associated ASD have a natural history and prognosis similar to that of an ASD alone. When symptoms develop, they do so in the third or fourth decade and are due to either right heart failure, pulmonary hypertension with cor pulmonale, or atrial arrhythmias.

Atrial arrhythmias may precipitate cardiac decompensation in patients with simple or complex PAPVC. The development of arrhythmias has been associated with both the size of the left-to-right shunt and the presence of pulmonary hypertension.[29] The incidence of arrhythmias increases with age in symptomatic patients and was found in 55% of patients older than 60 years undergoing operative correction for ASD with or without PAPVC.[39]

In the absence of an intracardiac communication, isolated PAPVC does not carry a risk of paradoxical systemic embolization. The absence of this risk factor must be considered in decisions regarding the need for operative intervention in patients with borderline hemodynamic criteria.

Medical Therapy

In asymptomatic patients who are not surgical candidates, no specific medical therapy is warranted. In older patients who develop symptoms of congestive heart failure, cor pulmonale, or arrhythmias, symptomatic relief can be obtained with the use of a diuretic, inotropic agent, and specific antiarrhythmic therapy.

Surgical Treatment

Surgical treatment of PAPVC should be considered in the following circumstances: 1) In the presence of a hemodynamically significant left-to-right shunt (Qp:Qs greater than 2:1, cardiomegaly on chest radiograph). This will include most patients with isolated PAPVC in which 50% or more of the pulmonary veins connect anomalously; 2) in patients with recurrent pulmonary infections in association with the Scimitar syndrome; 3) in conjunction with surgical repair of other major cardiac lesions (ASD, mitral stenosis); 4) when the anomalous connection affects surrounding structures by compression or obstruction. Although not previously reported in PAPVC, obstruction of the left main stem bronchus by an anomalous left vertical vein resulting in severe unilateral emphysema has been reported in total anomalous pulmonary venous connection.[48] In asymptomatic patients with PAPVC from a single lobe who do not fall into one of the above categories, surgical intervention is rarely indicated.

Although cardiac catheterization often is performed prior to operative correction, some patients may be candidates for surgical repair based on one or more noninvasive studies alone (echocardiography, radionuclide angiography). In patients with the typical clinical and echocardiographic findings of an atrial septal defect, Freed et al.[49] found no difference in operative morbidity or mortality in patients who did and in those who did not have preoperative cardiac catheterization. In that study, the diagnostic accuracy of noninvasive assessment compared favorably with invasive catheterization and angiography (85% vs. 90%). In the patients who had additional PAPVC undiagnosed prior to operation, all were discovered quickly at the time of surgery and repaired without major intraoperative problems.

The surgical technique for PAPVC varies and should be tailored to the anatomy involved and the associated intracardiac defects. The approach is usually through a midline sternotomy except in cases of anomalous venous connection to the inferior vena cava, in which case an extended thoracotomy is required. PAPVC to the right atrium usually is corrected in association with closure of an atrial septal defect. A patch of synthetic woven Dacron or pericardium is used to direct the anomalous veins through the right atrium to the atrial defect. At times, the atrial defect must be enlarged to facilitate this procedure.

When anomalous pulmonary venous connection to the superior vena cava is found, different surgical procedures have been recommended[50–53] because of the variable location and number of veins connected to the superior vena cava, the proximity of the sinus node to the area under consideration, and the propensity for development of pulmonary and systemic venous obstruction after this repair. Two major approaches include: 1) partitioning of the superior vena cava and approximation of the left lateral and caudal margins of the septal defect to the right atrial wall by direct sutures; 2) diversion of the anomalous flow by suturing a patch of pericardium or synthetic material around the opening of the anomalous veins and the margin of the septal defect.[54] To ensure unobstructed SVC flow, a free pericardial graft often is used as a gusset to enlarge the SVC/right atrial junction (Fig. 69–6). The right atrial appendage has been used as a flap to enlarge this area.

PAPVC to the inferior vena cava often is associated with anomalies of systemic arterial supply from below the diaphragm and pulmonary parenchymal abnormalities (sequestration). It is critical that the pulmonary arterial supply and pulmonary venous return be defined accurately prior to operative repair. Numerous reports of complete ligation of the entire venous return from the right lung during partial pneumonectomy for a sequestered lobe (many with lethal consequences) have been reported. In the usual circumstance, the common pulmonary vein is transected and reattached to the right atrial wall. An ASD is used or one is created; this vein is then connected to the left atrium by an intracardiac baffle using pericardium or synthetic material.

In most cases of PAPVC to the left innominate vein, the common trunk is mobilized and anastomosed directly to the left atrium or left atrial appendage. If this is done without extracorporeal circulation, the appropriate pulmonary artery must be occluded to prevent the development of severe pulmonary edema in the ipsilateral lung.

Outcome

Operative mortality in asymptomatic patients with PAPVC with or without an atrial septal defect is low and should parallel that of an ASD alone. Kyger et al.[38] reported no deaths in 109 patients operated on for sinus venosus ASD and PAPVC. Two other centers have reported no operative deaths in this lesion as well.[55,56]

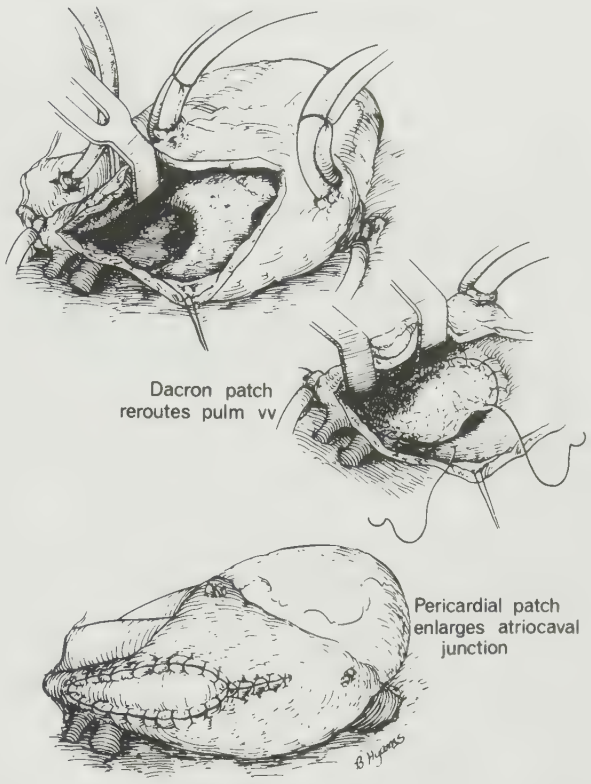

Fig. 69–6. Surgical repair of PAPVC associated with sinus venosus atrial septal defect. (Top) Atrial septal defect is visualized through the open right atrium. (Middle) Dacron patch closes the ASD and directs the two anomalous pulmonary veins to the left atrium. (Bottom) Pericardial patch is used to close the right atrium to avoid obstruction to the superior vena cava. (Reprinted with permission from Kyger, E.R., et al.: Sinus venosus atrial septal defect: Early and late results following closure in 109 patients. Ann. Thorac. Surg., 25:45, 1978.)

In older patients who have developed symptoms or who have elevated pulmonary vascular resistance, the operative risk is slightly increased. In a series of 66 patients older than 60 years undergoing operation for an ASD with or without PAPVC, the operative mortality was 6%.[39] In addition, an improvement in functional status was observed in 87% of survivors, including four of five with calculated pulmonary arterial resistance greater than eight units.

Late complications following surgery are rare. Obstruction to systemic or pulmonary venous return has been reported, usually in association with repair of PAPVC to the superior vena cava. Atrial tachy- and bradyarrhythmias also have been observed.

In summary, accurate diagnostic studies to include both precise delineation of the pulmonary venous anatomy and a functional assessment of the myocardium are required in patients with PAPVC in order to make reasonable and knowledgeable decisions concerning surgical intervention. In well-selected surgical patients, a good functional result can be realized and a normal or near-normal longterm outcome can be expected.

TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION

Total anomalous pulmonary venous connection (TAPVC) occurs when all pulmonary veins from both lungs drain into the right atrium or into a venous channel in communication with the right atrium. In all cases of TAPVC, systemic blood flow is maintained by way of right to left shunting through an atrial septal defect or, more commonly, a patent foramen ovale. In the group of patients with this abnormality, approximately one-third have other significant major cardiac malformations including single ventricle, atrioventricular canal defect, hypoplastic left heart, patent ductus arteriosus, and transposition of the great vessels.[57] Many patients in this group have been found to have abnormalities of atrial and visceral situs associated with the heterotaxy syndrome (asplenia and polysplenia). In two-thirds of cases, TAPVC occurs as an isolated abnormality associated with only an interatrial communication.

The incidence of TAPVC in autopsy series of patients dying of congenital heart disease varies from less than 1% in the study by Maude Abbott[58] to as high as 5%.[12] The incidence of TAPVC in the New England Regional Infant Cardiac Program[59] was 2.6%. The male to female sex ratio is equal in most cases of TAPVC; however, there is a strong male predominance (three to one) in infants with TAPVC of the infradiaphragmatic type.[60,61]

Genetics and Epidemiology

Because of the relatively low incidence of TAPVC in the spectrum of congenital heart disease, studies on genetic transmission of this defect are scarce. Paz and Castilla[62] reported three patients with TAPVC in one family. Results of chromosome studies of the three patients and the parents were normal. The authors speculated that the mechanism of transmission was either an undetectable small chromosome translocation or a single autosomal-dominant gene mutation with complete nonpenetrance in the parents. Most cases of TAPVC are sporadic and are likely due to a multifactorial inheritance pattern as described by Nora.[27] Although TAPVC often is associated with abnormalities of the asplenia and polysplenia syndromes, it is rare in other syndromes or in patients with chromosomal abnormalities.[63] TAPVC has not been associated with environmental teratogens nor is it associated with premature birth.[59]

Anatomy of TAPVC

A number of classification systems have been proposed to describe the different types of TAPVC, including one based on embryologic considerations according to Neill[11] and another based on the length of the anomalous channel and the size of the interatrial communication.[64] We will use the system described by Darling, Rothney, and Craig[12] to categorize TAPVC according to the anatomic location of the anomalous connection. Based on this system, the anatomic variations and the frequency with which they occur are as follows:

Type 1: anomalous connection at the supracardiac level (55%)
Type 2: anomalous connection at the cardiac level (30%)
Type 3: anomalous connection at the infracardiac level (13%)
Type 4: anomalous connection at two or more levels (2%)

From a functional standpoint, we will use the term *obstructed TAPVC* to denote impedance to pulmonary venous return occurring between the common pulmonary venous confluence and the right atrium. We will use the term *restrictive interatrial communication* to denote obstruction to blood flow from the right atrium to the left atrium and, hence, the systemic circulation. This distinction is important in understanding the altered hemodynamics observed and variations in clinical symptoms that occur in patients with this cardiac defect.

Supracardiac Type (Type 1)

This lesion is responsible for the majority of cases of TAPVC in most clinical and autopsy series. Connection to the left innominate vein is most common, accounting for 44% of all cases of TAPVC in the series by Darling.[12] In connections of this type, two pulmonary veins from each lung converge directly behind the left atrium and form a common pulmonary venous confluence. An anomalous vertical vein then arises from the left portion of the confluence and usually passes anterior to the left pulmonary artery and left mainstem bronchus on its course to the left innominate vein (Fig. 69–7A). The left innominate vein then empties normally into the right superior vena cava. Obstruction to pulmonary venous return is relatively uncommon in this lesion; when it occurs, it is due to either intrinsic narrowing or extrinsic compression of the anomalous vertical vein. Intrinsic narrowing occurs either at the origin of the ascending vein or at the insertion of this vein in the innominate vein. Extrinsic compression is found in cases in which the anomalous vertical vein courses between the left pulmonary artery anteriorly and the left mainstem bronchus posteriorly.

Anomalous connection to the right superior vena cava occurs much less frequently and often is associated with complex cardiac malformations.[65] The anomalous venous trunk arises from the right side of the confluence, ascends anteriorly to the hilus of the right lung and enters the posteromedial aspect of the superior vena cava. The entrance to the SVC usually is separate from the azygous vein, although instances of anomalous connection to the azygous vein have been reported. Obstruction may occur by extrinsic compression of the anomalous ascending vein between the right pulmonary artery and the trachea or may occur where the ascending vein enters the superior vena cava.

Cardiac Type (Type 2)

Under these circumstances, the pulmonary veins connect at the level of the coronary sinus or in the posterior-right atrium near the midatrial septum. The anomalous veins may connect by a short common channel or may connect by three or four separate openings (Fig. 69–7B,B′). In TAPVC to the coronary sinus, the coronary sinus ostium is enlarged dramatically but normally placed between the entrance of the inferior vena cava and tricuspid valve (Fig. 69–7C). The great cardiac vein drains into this enlarged ostium of the coronary sinus and hence to the right atrium.

Many authors have considered obstruction to pulmonary venous return[66,67] to be rare in patients with direct cardiac connections. Recent data suggest, however, that obstruction to pulmonary venous return may be more common than previously appreciated in this anatomic subgroup. Jonas and colleagues[68] found obstruction in 22% of unoperated and operated patients with TAPVC to the coronary sinus. They observed that obstruction occurred when a very short, narrow segment of a common vertical vein connected the horizontal right and left pulmonary veins to the ostium of the

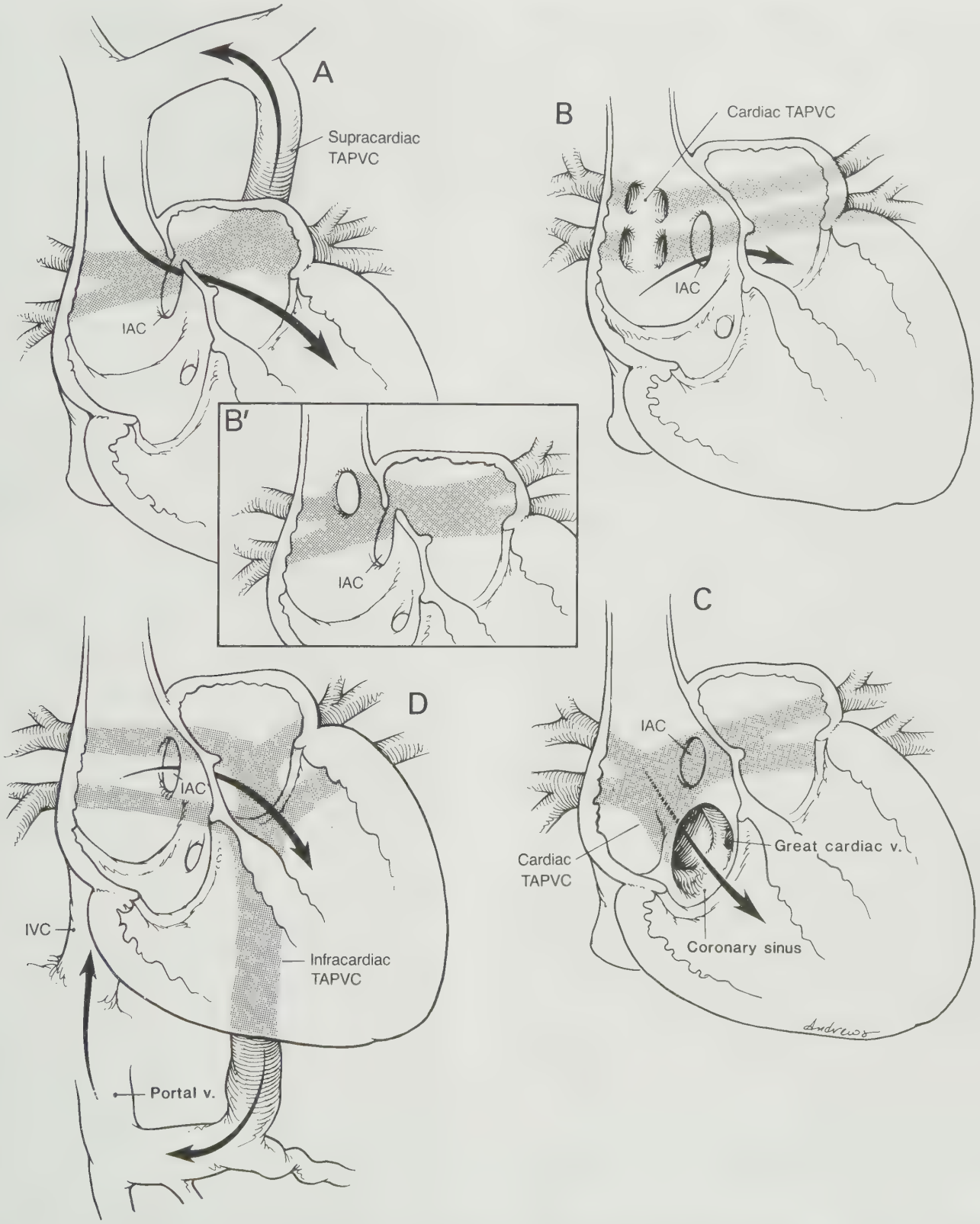

Fig. 69–7. Types of total anomalous pulmonary venous connection. (A) Supracardiac connection to left innominate vein. (B) Cardiac connection via four separate veins. (B[1]) Cardiac connection by single common orifice. (C) Cardiac connection to coronary sinus. (D) Infracardiac (subdiaphragmatic) connection to portal system. (Adapted from Reardon, M.J., et al.: Total anomalous pulmonary venous return: Report of 201 patients treated surgically. Texas Heart Inst. J., *12*:131, 1985.)

coronary sinus. Obstruction also has been reported in the individual pulmonary veins on entering the common venous channel due to intimal proliferation,[69] a finding not unlike that observed in isolated pulmonary vein stenosis.

Infracardiac Type (Type 3)

Anomalous pulmonary venous connection of this type also has been referred to as infradiaphragmatic TAPVC. This type of connection almost always is associated with a severe degree of obstruction to pulmonary venous return and most often causes symptoms very early in the newborn period. Usually, the pulmonary veins from both lungs converge to a confluence directly behind the left atrium. From this confluence, a descending vein courses anterior to the esophagus and traverses the diaphragm through the esophageal hiatus (Fig. 69–7D). In the majority of patients (70 to 80%),[12,61] this anomalous descending vein then joins the portal venous system, either at the splenic vein or at the confluence of the splenic and superior mesenteric veins. The descending vein may, on occasion, connect directly to the ductus venosus. Rarely, the connection is to one of the hepatic veins or to the inferior vena cava.[61] There are, however, variations of this pattern. The most common is a long vertically oriented common pulmonary venous chamber with insertion of the pulmonary veins from the lower segments of each lung occurring near the esophageal hiatus some distance from the upper lobe pulmonary veins.

Obstruction to pulmonary venous return may occur at a number of sites along the anomalous venous pathway. *Discrete obstruction* due to intrinsic narrowing or extrinsic compression may occur 1) at the level of the esophageal hiatus, 2) at the junction of the descending vein/portal vein connection, or 3) at the ductus venosus after constriction or closure of this vessel. In addition, *diffuse obstruction* occurs when pulmonary venous blood entering the portal circulation must traverse the hepatic sinusoids. Thus, the length of the anomalous venous channel and the large number of possible sites for pulmonary venous obstruction predicts that most patients with infracardiac TAPVC will manifest symptoms very early in the newborn period.

Mixed Type (Type 4)

This variation of total anomalous pulmonary venous connection occurs in fewer than 5% of reported series.[12] The most common pattern of mixed TAPVC involves drainage of the left lung through a vertical vein to the left innominate vein, and the right lung connected either to the right atrium or coronary sinus. Rarely, the veins from the right lung will connect infradiaphragmatically to the portal vein. Mixed TAPVC is associated more commonly with other major cardiac anomalies.[2] As described previously, obstruction at one or more veins can occur in this type of anomaly; the type and location depend on the site of anomalous connection.

Associated Cardiac Anomalies

Total anomalous pulmonary venous connection with significant other cardiac anomalies occurs in approximately one-third of patients. These associated defects include single ventricle, truncus arteriosus, transposition of the great arteries, pulmonary atresia, coarctation of the aorta, and anomalies of systemic venous return.[34] The hemodynamic abnormalities observed in patients with complex TAPVC are related both to the TAPVC itself (with or without obstruction) and to the predominant associated cardiac defect. Hemodynamic interactions between defects may occur and, at times, lead to confusing clinical signs and symptoms. An example of this is occult pulmonary venous obstruction in patients with TAPVC and marked decrease in pulmonary blood flow (severe pulmonary stenosis or atresia). Under these circumstances, pulmonary venous obstruction may be subclinical until pulmonary blood flow is augmented by medical or surgical therapy.

Total anomalous pulmonary venous connection occurs commonly in patients with abnormalities in atrial and visceral situs (asplenia and polysplenia syndromes). Asplenia, or right isomerism, is associated with the presence of two atrial chambers, both of which have right atrial morphology. This developmental complex usually is accompanied by a complete atrioventricular canal defect, single ventricle, pulmonary stenosis or atresia, and malposition of the great vessels. Because this type of heart lacks a morphologic "left atrium," TAPVC occurs in all of these patients. The pulmonary venous connection pattern commonly found in patients with right isomerism is depicted in Figure 69–8. The pulmonary veins connect to a pulmonary venous confluence, which then drains to either the right or left superior vena cavae or directly to the morphologic right atria through a single orifice.[70] Common associated noncardiac malformations include bilateral morphologic right lungs, abdominal visceral heterotaxia, and malrotation abnormalities of the gastrointestinal tract.

In contrast, patients with the polysplenia syndrome (left isomerism) have bilateral morphologic left atria and, in most circumstances, less severe associated cardiac defects. Pulmonary venous connection may occur to either the right- or left-sided atrium. In most cases, however, the right pulmonary veins connect to the right-sided atrium and the left veins to the left-sided atrium. Although some embryologists would argue that TAPVC does not exist in polysplenia (all pulmonary veins connect to a morphologic left atrium), we prefer to consider this an abnormality of pulmonary venous connection because of the obvious surgical implications.

Asplenia and polysplenia syndromes will be discussed in depth in Chapter 75. The next discussion focuses primarily on TAPVC

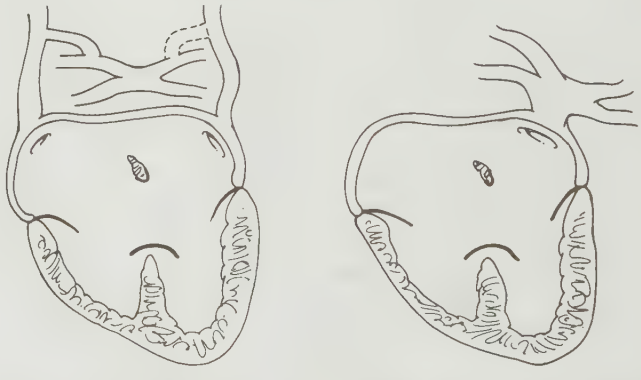

Fig. 69–8. Pulmonary venous connection pattern found in patients with right atrial isomerism. The pulmonary veins connect to a pulmonary venous confluence, which then drains to either of the superior cavae (left) or to either of the morphologic right atria (right). (Reprinted with permission from Huhta, J.C.: Pediatric Imaging/ Doppler Ultrasound of the Chest. Philadelphia, Lea & Febiger, 1986, p. 150, Figure 10–4.)

as an isolated abnormality (with only the obligatory atrial septal defect) not associated with complex cardiac disease.

Pathophysiology

The primary physiologic derangement in patients with TAPVC is mixing of both pulmonary venous and systemic venous blood in the right atrium. From the right atrium, this mixed venous blood is distributed either to the systemic circulation by an obligatory interatrial communication, or to the pulmonary circulation by the right ventricle and pulmonary artery. The factors that determine blood flow distribution in these two circuits and, thus, the predominant clinical symptoms include 1) the presence and severity of obstruction in the extracardiac pulmonary venous channels and 2) the relative size of the interatrial communication. Although these two factors are not mutually exclusive in a given patient, one usually is predominant and determines the clinical course. Therefore, we will discuss each separately.

TAPVC with Obstruction in the Pulmonary Venous Channels

Obstruction in the pulmonary venous channels usually is due to *discrete intrinsic narrowing* of the vessel itself or to *extrinsic compression* by surrounding structures. In addition, some authors think the length of the anomalous venous channel affects blood flow in the pulmonary venous system, with longer channels resulting in greater degrees of impedance to pulmonary venous return.[64] Another source of obstruction in patients with infradiaphragmatic TAPVC occurs when the descending anomalous vein drains into the portal venous system and must traverse the hepatic sinusoids.

In all cases of obstruction to pulmonary venous return, pulmonary venous pressures become elevated. This elevation of pressure is transmitted to the capillary bed and results in progressive interstitial and alveolar edema. Compensatory mechanisms are invoked to minimize this increased lung water and include increase in pulmonary lymph flow, recruitment of alternate pulmonary venous–bronchial venous anastomoses, and reflex pulmonary vasoconstriction.[34] With this marked increase in pulmonary resistance, the right ventricular systolic and end-diastolic pressures increase; the right ventricular compliance decreases; impedance to right ventricular filling occurs; and pulmonary blood flow diminishes. Elevation in right atrial pressure leads to an increase in right-to-left shunt across the interatrial communication and progressive systemic hypoxemia. The right-to-left shunt allows decompression of the right atrium and right ventricle; for this reason the heart is not usually enlarged on chest radiograph. If the ductus arteriosus remains patent, predominant right-to-left shunting occurs, thereby increasing pulmonary oligemia. Progressive systemic hypoxemia leads to metabolic acidemia and multisystem organ failure. Without relief of the obstruction in the anomalous venous channel, death ensues. The size of the interatrial communication (whether a patent foramen ovale or an atrial septal defect) probably does not influence the outcome in these patients.

Because of prominent right-to-left shunting at both the atrial and ductal level and the ensuing severe hypoxemia, TAPVC with obstruction often is confused with persistent fetal circulation if the pulmonary veins are not delineated thoroughly during echocardiographic examination.

TAPVC with a Restrictive Interatrial Communication

Some type of interatrial communication (IAC) is needed to maintain systemic blood flow in patients with TAPVC. The size of this communication plays a critical role in the distribution of mixed venous blood between the pulmonary and systemic circulations in the absence of significant obstruction in the pulmonary venous channels. A patent foramen ovale is found in 70 to 80% of infants with uncomplicated TAPVC[12,64,71] and imposes some degree of restriction to left atrial and left ventricular filling in the majority of infants.[71] The remaining patients have a nonrestrictive IAC, usually an atrial septal defect of the secundum type. The postnatal hemodynamics and clinical course are different, depending on whether the IAC is restrictive.

Blood flow across the foramen ovale in the fetus with TAPVC is only mildly increased due to the normally high pulmonary vascular resistance and the relatively small amount of pulmonary venous blood returning anomalously to the right atrium. The stimulus for development of a large IAC, as would be present in patients with right heart obstructive lesions (tricuspid atresia, pulmonary atresia with intact ventricular septum), therefore does not occur. Soon after birth, systemic cardiac output is maintained across this adequate IAC. However, as pulmonary vascular resistance diminishes and pulmonary blood flow increases, right ventricular filling is enhanced. Blood returning to the right atrium is shunted preferentially away from the high-resistance foramen ovale. With rapid growth in the first few weeks and months of life, demands for systemic output increase and cannot be met because of the non-restrictive interatrial communication. Massive pulmonary overcirculation in the face of a fixed systemic cardiac output leads to progressive cardiopulmonary dysfunction. We have observed that symptomatic congestive heart failure does not occur in the first few days and weeks of life in infants with nonobstructed TAPVC and a restrictive IAC, but develops in the second month of life and can be partially or totally relieved by transvenous atrial septostomy.[71]

Elevation of right atrial pressure occurs in response to the restrictive IAC and leads to both systemic and pulmonary venous congestion. Pulmonary blood flow ranges from 1.5 to 5 times systemic flow and results in marked right ventricular dilatation and displacement of the interventricular septum into the left ventricular cavity. Pulmonary arterial pressure was greater than one-half systemic pressure in all patients in our study.[71] The elevation of pulmonary arterial pressure in infants with a restrictive IAC usually is due to torrential pulmonary blood flow rather than elevation of pulmonary vascular resistance. Histologically, the muscular pulmonary arteries and arterioles have only medial hypertrophy. Mild proliferative intimal lesions may occur in the young infant but are more common in the older child and adult.

Volume of the left atrial chamber approximates 50% of normal[20,72] due to the absence of that volume contributed by the common pulmonary vein. The ventricular cavity size and left ventricular volume is decreased,[72,73] although the mass of the left ventricle is normal.[73] The decrease in left ventricular cavity size is due largely to the abnormally displaced interventricular septum and the chronic decrease in left ventricular preload. Systemic cardiac output, when measured, is usually low due to inadequate preload and a decrease in left ventricular ejection fraction.[21,72,73]

Systemic oxygen saturation in most patients is 85 to 90%, re-

flecting a large pulmonary blood flow in the setting of complete admixture of pulmonary and systemic venous return. Oxygen saturation in the pulmonary artery may be significantly greater than that found in the femoral artery in patients with supracardiac and cardiac anomalous venous connections. This difference may be due to the streaming effect of inferior vena caval blood through the foramen ovale with pulmonary venous blood returning through either the SVC, right atrium, or coronary sinus being preferentially directed across the tricuspid valve.[71,66]

TAPVC with a Nonrestrictive Interatrial Communication

A nonrestrictive IAC occurs in approximately 20% of patients with uncomplicated TAPVC. In the absence of obstruction in the extracardiac pulmonary venous channels, these patients usually exhibit hemodynamic findings and clinical symptoms different from the above two groups.

The nonrestrictive interatrial communication allows free communication between the two atria and, under these conditions, the distribution of mixed venous blood is determined by the relative compliance of the atria and ventricles and on the relative resistances in the pulmonary and systemic arterial circulations.

The systemic blood oxygen saturation in this "total mixing lesion" is dependent, for the most part, on the pulmonary blood flow. Since in most circumstances the systemic blood flow is 3 L/min/m^2, this is the systemic venous return that mixes with the pulmonary venous return: the higher the pulmonary blood flow (and, therefore, pulmonary venous return) the closer to the pulmonary venous saturation will be the "totally mixed" blood that passes across the IAD into the left side of the heart and out the aorta. For example, if we assume for this purpose that the mixed venous O_2 saturation is 65% and the systemic blood flow is 3 L/min, then if the pulmonary blood flow is 3 L/min, the systemic O_2 saturation (mixing equal parts of 95% and 65%) is 80%; if the pulmonary blood flow is 6 L/min, the systemic O_2 saturation is 85%.

Although a large left-to-right shunt invariably develops, pulmonary artery pressures are usually normal or only mildly elevated.[71,74] The severe hemodynamic disruption and clinical symptoms seen in patients with a restrictive IAC usually are not observed. The gross pathologic changes as previously described in patients with a restrictive IAC occur but are less striking. A number of these patients will have a clinical course not unlike that of a large atrial septal defect in which signs of right heart failure and/or pulmonary hypertension may not develop until after the third or fourth decade of life.

Clinical Features

The natural history of clinical signs and symptoms and the subsequent hemodynamic observations in patients with TAPVC can be related to the previously described pathophysiologic categories.

TAPVC with Obstruction in the Anomalous Pulmonary Venous Channel

Signs and Symptoms. Infants born with obstruction in the anomalous pulmonary venous channels develop symptoms shortly after birth or within the first day or two of life. Cyanosis and respiratory distress usually occur early and may be severe. In patients with anomalous connection below the diaphragm, feeding may acutely worsen symptoms of cyanosis and dyspnea due to increased intraabdominal pressure or possibly impingement of the dilated esophagus on the common pulmonary vein as it traverses the esophageal hiatus. Severe pulmonary hypertension leads to progressive decrease in pulmonary blood flow and severe hypoxemia. If not treated, most infants die in the first few days or weeks of life, although some may live for 3 to 4 months.[60]

Physical Examination. Physical examination reveals a severely cyanotic infant with moderate to marked respiratory distress. The heart is not enlarged clinically, although there is usually a prominent right ventricular impulse, which suggests pulmonary hypertension. The pulmonic component of the second heart sound may be accentuated, and there may be a third or fourth heart sound audible over the left lower sternal border. Murmurs are infrequent and, when present, usually are detected over the pulmonary outflow tract. The murmur of tricuspid insufficiency may be appreciated due to right ventricular hypertension. Peripheral pulses are usually of normal amplitude shortly after birth but may weaken as progressive cardiac failure ensues. Hepatomegaly is present and often quite dramatic in patients with anomalous pulmonary venous connection to the portal venous system.

Electrocardiogram. Right ventricular hypertrophy is observed in the majority of patients with obstructed TAPVC, usually manifested by a qR pattern in the right chest leads. In addition, many patients exhibit a paucity of left ventricular forces in the left precordial leads. Right atrial enlargement is rare.

Radiographic Features. The chest roentgenogram may be quite helpful in determining the presence or absence of obstruction to pulmonary venous return in patients with suspected TAPVC.[75] The cardiac size is usually normal or only mildly increased. Pulmonary vascular markings, however, are abnormal and are characterized by a diffuse, linear reticular pattern radiating from the hilar regions (Fig. 69–9). Overt pulmonary edema with Kerley B

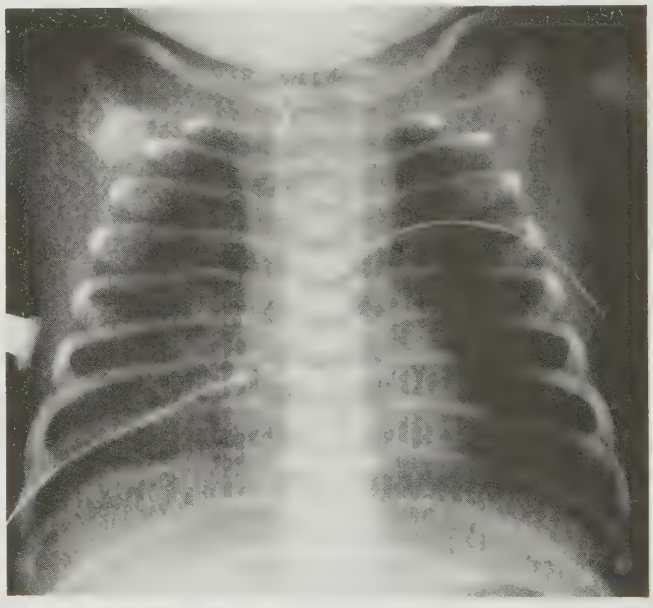

Fig. 69–9. TAPVC with obstruction. The heart size is normal, and the lungs are hyperinflated. Pulmonary vascularity demonstrates a diffuse, linear reticular pattern radiating from the hilum, which represents pulmonary venous engorgement and lymphatic distension.

lines may be present with perihilar congestion, which results in obscured cardiac borders. Hyperinflation of the lungs may be seen, which should differentiate this cardiac anomaly from early hyaline membrane disease. In addition, the normal to increased pulmonary vascularity helps distinguish this entity from persistent fetal circulation syndrome.

TAPVC with a Restrictive Interatrial Communication

Signs and Symptoms. These patients are usually asymptomatic at birth and during the first few weeks of life. When signs or symptoms are detected during this period, they are usually mild cyanosis with crying or mild tachypnea during feedings. As pulmonary blood flow increases and the interatrial communication becomes restrictive, symptoms of progressive tachypnea, respiratory distress, feeding difficulties and cardiac failure occur. These symptoms usually develop after the first month of life and lead to medical consultation in the second month. In the absence of medical or surgical intervention, progressive cardiac failure complicated by pulmonary infections occurs, which is fatal in 75 to 85% of these infants prior to 1 year of age.[64,76]

Physical Examination. In symptomatic infants, failure to thrive, resting tachypnea, and mild perioral duskiness are observed. Overt cyanosis may be absent due to relatively high arterial oxygen saturations. There is a prominent right ventricular lift and a hyperdynamic precordium. Auscultation reveals a loud first heart sound and at times a systolic ejection click. The second heart sound usually is widely split and fixed and the pulmonary component is often accentuated. An S3 gallop over the left lower sternal border and apex may be detected, and a fourth heart sound may be heard as well.

A low-frequency systolic murmur of Grade I to II in intensity representing increased pulmonary flow usually is heard over the left upper sternal border. In addition, there is a tricuspid diastolic murmur at the left lower sternal border in approximately 50% of patients.[76] Occasionally, a continuous venous hum may be detected in an area overlying the anomalous venous connection. This murmur has been found most commonly in patients with supracardiac TAPVC and is distinguished from the innocent venous hum by its lack of variation with change in position or jugular venous pressure. Hepatomegaly is usual, and peripehral edema often is observed.

Electrocardiogram. Right axis deviation, right atrial enlargement, and right ventricular hypertrophy are seen in most patients who are symptomatic. The electrocardiogram is often normal in patients in the first week of life, reflecting the minimal hemodynamic disturbance at this stage.[71]

Radiographic Features. The chest roentgenogram may be normal in the first week of life.[71] When symptoms develop, the heart size is moderate to markedly increased with cardio-thoracic ratios between 0.60 and 0.70.[77] This enlargement is due to right atrial and right ventricular dilatation. The pulmonary vascularity is increased diffusely, and there is dilatation of the hilar and midlung vessels.

Distinctive radiographic features may be observed, reflecting the course of the anomalous pulmonary venous channel. The classic figure-eight or "snowman" sign in TAPVC to the left innominate vein may be seen in the older infant and child (Fig. 69–10), although it has been observed in patients as young as 4 months of age.[78] The right superior mediastinum may be prominent in

Fig. 69–10. Supracardiac TAPVC. Chest radiograph in a child with connection to the left innominate vein demonstrating increased pulmonary vascularity and the figure-eight or "snowman" appearance. Arrow points to anomalous vertical vein.

cases of TAPVC to the superior vena cava. Gott and associates[79] described the radiographic feature of horizontal takeoff of the left border of the heart below the aortic arch. This box-like appearance was due to massive enlargement of the right atrium and right ventricle with the latter structure forming most of the upper left border of the cardiac silhouette.

TAPVC with a Nonrestrictive Interatrial Communication

Signs and Symptoms. Patients with a nonrestrictive interatrial communication exhibit a different pattern of clinical symptoms. When symptoms develop in the first year of life, they consist of mild failure to thrive, exertional dyspnea, and recurrent pulmonary infections. Clinical cyanosis is rare in the first 1 or 2 years of life but may become apparent in the older child or young adult with the development of right heart failure or, rarely, pulmonary vascular obstructive disease.

Physical examination and cardiac auscultatory findings may be similar to those just described in patients with a restrictive interatrial communication or may mimic more closely those observed in a large atrial septal defect. Electrocardiography demonstrates right atrial enlargement and right ventricular hypertrophy. Radiographic findings include mild to moderate cardiomegaly with increased pulmonary vascularity and the radiographic appearance of the specific anomalous venous channel as discussed previously.

In summary, patients with TAPVC and a nonrestrictive interatrial communication have signs and symptoms that fall between, on the one hand, patients with a large uncomplicated atrial septal defect and, on the other, those with TAPVC with a restrictive IAC and congestive heart failure.

Diagnostic Techniques

Echocardiography

The M-mode echocardiographic findings in TAPVC include moderate to marked dilatation of the right ventricle, paradoxical ventricular septal motion and, on occasion, demonstration of an

echo-free space posterior to the left atrium representing the pulmonary venous confluence.[80,81] High-resolution real-time two-dimensional echocardiography with Doppler capabilities has extended this modality to the degree that precise anatomic and functional characterization of each type of TAPVC can be accomplished in many cases.

Two-dimensional imaging of the anomalous pulmonary venous pathways has now been well described.[82–85] The development of multiple imaging planes to reconstruct the course and connections of the anomalous pulmonary venous channels has led to precise anatomic localization that may, in selected cases, obviate the need for invasive cardiac catheterization.

The parasternal long axis scan may reveal the confluence of the pulmonary veins posterior to the left atrium, or it may detect a prominent coronary sinus (Fig. 69–11). Right ventricular enlargement with septal displacement to the left and enlarged pulmonary arteries are common. Apical and subcostal four-chamber views may demonstrate the individual pulmonary veins connecting to the confluence and the subsequent entrance to the right atrium or coronary sinus. Subcostal transverse and sagittal scans of the abdomen are used to image the descending vein in patients with infradiaphragmatic TAPVC[82] (Fig. 69–12). Suprasternal scanning, using long and short axis planes, is useful in detection of the pulmonary venous confluence in supracardiac TAPVC. However, mapping the course of the subsequent drainage often requires multiple projections (Fig. 69–13). The suprasternal short axis scan may be used to detect the points of insertion of the individual pulmonary veins into the venous confluence in patterns with infradiaphragmatic TAPVC.

Using a standardized sequential technique with imaging in multiple planes as just described, Huhta et al.[70] prospectively detected the presence of TAPVC in 33 of 34 patients undergoing cardiac catheterization (97% sensitivity). However, the exact type of TAPVC and the site (or sites) of anomalous connection was accurately predicted in only 71%. Errors in localization of the anomalous pulmonary venous connection occurred in circumstances of abnormal atrial situs associated with complex congenital heart disease and in patients with mixed type TAPVC.

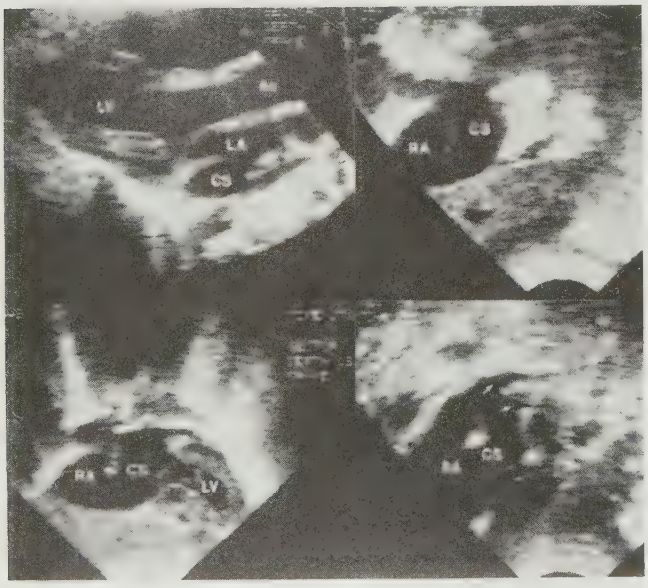

Fig. 69–11. Ultrasonic imaging of total anomalous pulmonary venous connection to the coronary sinus. Long axis scans show a markedly dilated coronary sinus behind the left atrium (left upper panel). Imaging of the entry of the pulmonary veins into the coronary sinus (white arrows) is possible from subcostal scans. (Reprinted with permission from Huhta, J.C.: Pediatric Imaging/Doppler Ultrasound of the Chest. Philadelphia, Lea & Febiger, 1986, p. 155, Figure 10–8, from Br. Heart J., *53*:525, 1985.)

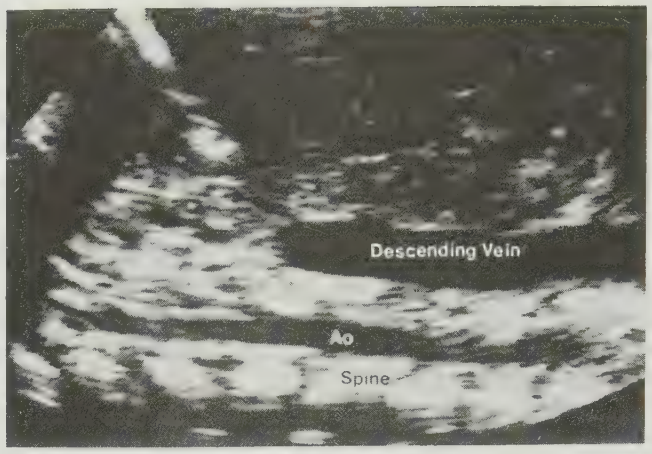

Fig. 69–12. Sagittal scan of the abdomen showing the descending aorta, spine, and more anterior descending vein entering the liver. (Reprinted with permission from Huhta, J.C.: Pediatric Imaging/Doppler Ultrasound of the Chest. Philadelphia, Lea & Febiger, 1986, p. 158, Figure 10–11.)

The addition of both pulsed and continuous-wave Doppler ultrasound has enhanced diagnostic accuracy of two-dimensional imaging alone. Stephenson et al.[86] used pulsed Doppler echocardiography from the parasternal and suprasternal planes to diagnose supracardiac TAPVC to the innominate vein. The Doppler flow pattern consisted of nonphasic disturbed flow posterior to the left atrial line detected by the M-mode technique. Stephenson et al. observed that the abnormal flow pattern differed from left atrial flow in its directionality (away from the heart) and its characteristic poor variation with changes of cardiac cycle. This characteristic Doppler flow pattern has now been used to detect all types of TAPVC, both above and below the diaphragm.[87,88] Smallhorn and Freedom[89] described the Doppler flow pattern observed in TAPVC with extracardiac obstruction as nonphasic and varying only with respiration. Vick et al.[90] thought that a disturbed venous flow pattern with a peak velocity of greater than 2 m/s occurring in diastole at the site of narrowing was associated with significant obstruction to pulmonary venous return.

Radionuclide Angiography

Radionuclide imaging has been used in the noninvasive assessment of TAPVC.[91] In four patients with infradiaphragmatic TAPVC, rapid recirculation through the right atrium occurring 3 to 6 seconds after the initial passage of radionuclide was recorded. In addition, direct visualization of the anomalous common pulmonary trunk was observed in three of four patients. In these patients, this technique was helpful in differentiating TAPVC from persistent fetal circulation. First-pass radionuclide angiography may aid the preoperative quantitation of pulmonary to systemic

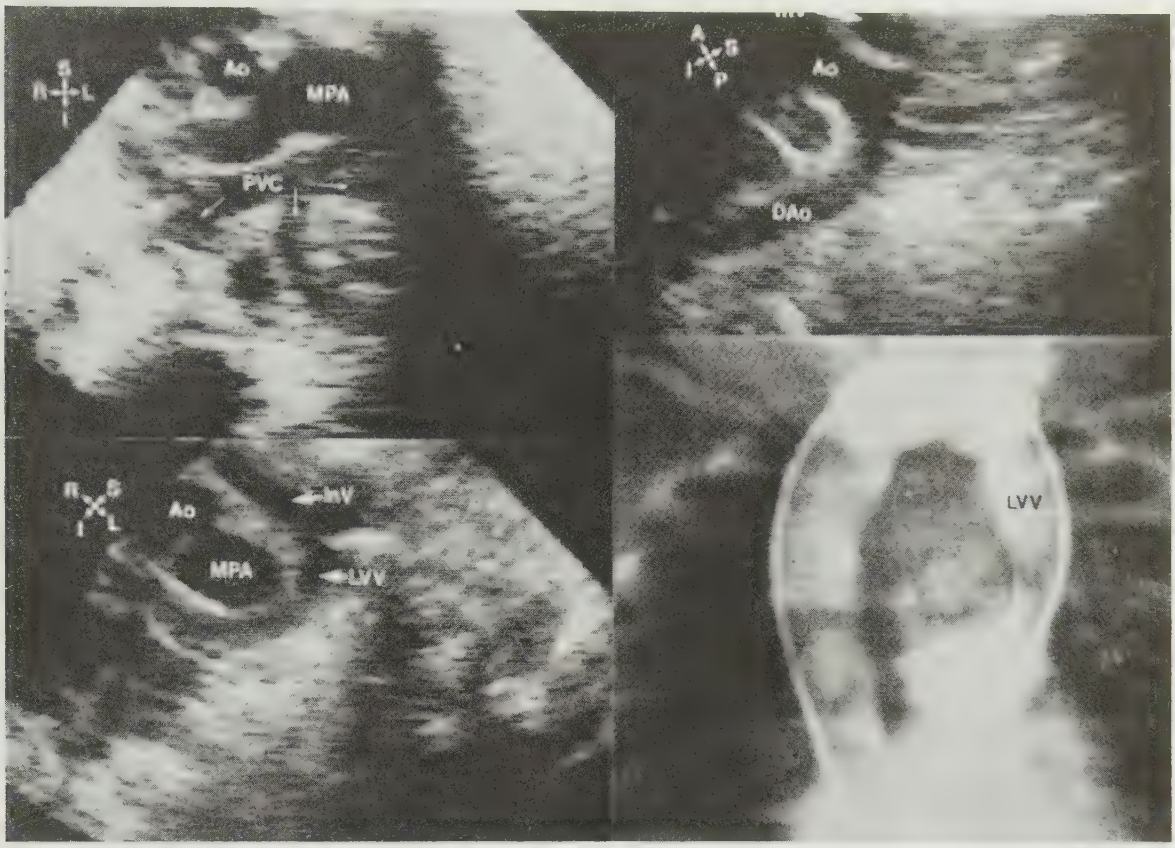

Fig. 69–13. Total anomalous pulmonary venous connection to a left vertical vein in an infant. Suprasternal scans reveal the entry of the four pulmonary veins to the pulmonary venous confluence (PVC) (left upper panel), and segmental imaging of the vertical vein and innominate vein (InV) confirm the diagnosis. An angiogram with the catheter in the left vertical vein (LVV) is shown for comparison (right lower panel). (Reprinted with permission from Huhta, J.C.: Pediatric Imaging/Doppler Ultrasound of the Chest. Philadelphia, Lea & Febiger, 1986, p. 154.)

blood flow ratios and the postoperative assessment of residual defects and ventricular function.

Cardiac Catheterization

Catheter Course. The catheter course in combination with oxygen-saturation data may be diagnostic of TAPVC if the anomalous pulmonary venous channel is entered directly. This can be accomplished usually with connection to the right atrium and coronary sinus as well as supracardiac connection to the left innominate vein. Catheter manipulation into the anomalous connection to the superior vena cava may be difficult due to the acute angle of insertion of the anomalous vein and the high frequency of obstruction that occurs in this type of connection. Although rare, the descending anomalous venous connection in patients with infradiaphragmatic TAPVC may be entered during catheter manipulation through the umbilical vein.

Saturations. Sampling of blood in the right atrium usually reveals oxygen saturations above 90%. Although one would expect saturations to be nearly identical in all cardiac chambers and great vessels distal to the right atrium, we[71] and others[66,92,93] have noted significant differences in the pulmonary arterial and systemic arterial oxygen saturations in many patients. In cases of cardiac or supracardiac TAPVC, pulmonary venous blood is directed preferentially across the tricuspid valve whereas inferior vena caval flow is directed across the foramen ovale; this leads to significantly lower saturations in the systemic arterial circulation when compared to those found in the pulmonary artery. Conversely, significantly higher oxygen saturations may be found in the systemic arterial system in patients with infradiaphragmatic TAPVC. Oxygen tensions (Pa_{O_2}) as high as 250 mm Hg have been described in patients breathing 100% oxygen with infracardiac TAPVC due to this streaming effect.[93,94] Such high saturations may be misleading and may erroneously suggest the diagnosis of persistent fetal circulation or primary pulmonary disease.

Hemodynamic Data. In patients with severe obstruction in the extracardiac pulmonary venous channels, pressures in the right ventricle and pulmonary artery are equal to or greater than systemic. Pulmonary artery wedge pressure is elevated, in contrast to the relatively normal or low left atrial pressure. Right atrial pressure is usually normal although it may be elevated. Entering the common pulmonary venous channel directly with a slow pullback pressure tracing often reveals a discrete pressure gradient at the site of obstruction.

Patients with a restrictive IAC have elevated pulmonary artery pressures that range from 50% to 100% of systemic pressure.[71] This pulmonary hypertension is of the high flow–low resistance type and can be reduced significantly by creating an adequate interatrial communication (Fig. 69–14). The right atrial mean and phasic pressures may be elevated over those found in the left atrium. In these cases, a restrictive interatrial communication is

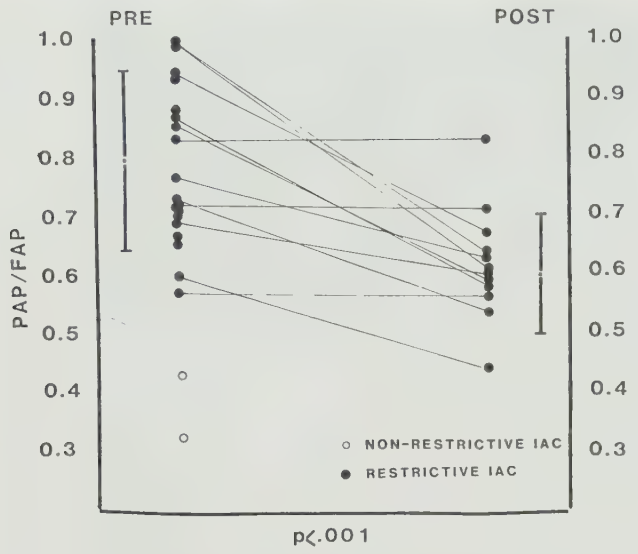

Fig. 69–14. Atrioseptostomy in TAPVC with a restrictive interatrial communication. The systolic pulmonary artery (PAP) to femoral artery (FAP) pressure ratio decreases significantly after an adequate septostomy. (Reprinted with permission from Ward, K.E., et al.: Restrictive interatrial communication in total anomalous pulmonary venous connection. Am. J. Cardiol., *57*:1131, 1986.)

diagnosed easily. When the atrial pressures are nearly equal, our experiences[71,92,95] and that of others[69] suggest that there still may be significant obstruction at the atrial septum. This phenomenon likely is related to several factors, including: 1) the greater capacitance of the right atrium as compared to the left[92]; 2) the possibly comparable compliance of the two ventricles and thus their equal respective filling pressures; 3) the technical difficulty of detecting transient, phasic pressure differences in patients with rapid heart rates using standardized fluid-filled catheter systems. To rule out completely a restrictive interatrial communication, measurement of the size of the atrial defect is mandatory and is accomplished by slow withdrawal of a calibrated septostomy balloon from left atrium to right atrium. An interatrial communication less than 10 mm by this method should be suspected as being restrictive.[71]

Intermediate degrees of obstruction in the pulmonary venous channels may exist and may be related to the length of the anomalous channel. This situation occurs commonly in TAPVC to the left innominate vein in which a gradual mean pressure gradient as great as 12 mm Hg may be recorded between the common pulmonary vein and right atrium. Although a number of these patients may respond favorably to balloon septostomy, 50% of the infants in our study with this anatomic variant failed to demonstrate adequate relief of symptoms after septostomy and required early surgical repair.[71]

Angiography. Selective right and left pulmonary arteriography is the initial angiogram performed in most patients with suspected TAPVC. On the levophase, collection of the contrast material in the pulmonary venous channels usually demonstrates the site of connection and areas of potential obstruction.

In patients with obstructed TAPVC and severe pulmonary hypertension, pulmonary angiography may be difficult because of prominent right-to-left shunting through the ductus arteriosus. Under these circumstances, balloon occlusion of the ductus during angiography may be used to enhance visualization of the anomalous venous connections. With severe obstruction, circulation time through the lungs is prolonged, and contrast material is slow to fill the pulmonary venous circuit, thereby resulting in poor opacification. In these cases, direct injection in the pulmonary artery wedge position through an end-hole catheter has been used to enhance definition of pulmonary venous anatomy.

With manipulation of the catheter directly into the anomalous venous channels, angiography can be more rewarding and detect abnormalities not observed during follow-through pulmonary arteriography.

Balloon Atrioseptostomy. Although some investigators feel that significant obstruction at the atrial level (restrictive IAC) is rare in TAPVC,[66] we[71] and others[64,69] have found hemodynamic or anatomic evidence of a restrictive IAC in 70 to 80% of patients with uncomplicated TAPVC. Creation of a large IAC by open septectomy[74] or balloon/blade septostomy[71,92,95–97] is effective in improving hemodynamics and clinical symptoms in most patients with congestive heart failure due to a restrictive IAC.

If a significant atrial pressure difference exists, septostomy results in equalization of mean and phasic pressures in most cases. In addition, the pulmonary artery/femoral artery pressure ratio is reduced significantly due to both a decrease in pulmonary arterial blood flow and an increase in systemic flow. These favorable alterations persist in longterm followup studies, and the pulmonary artery/femoral artery pressure ratio may show progressive reduction over that observed in the early postseptostomy period. Clinical improvement occurs in most patients and may be dramatic in some.

Performing balloon/blade septostomy in TAPVC is challenging due to the small size of the left atrium and the absence of normal left atrial landmarks (pulmonary veins, high oxygen saturations). In addition, rapid inflation and pullback must be performed since the inflated balloon obstructs the entire systemic output. Echocardiographic imaging during balloon placement and inflation has been helpful in this regard.

Differential Diagnosis

In newborn infants with obstructed TAPVC, the differential diagnosis includes other causes of pulmonary venous obstruction (atresia of the common pulmonary vein, pulmonary vein stenosis, cor triatriatum), hypoplastic left heart syndrome, tricuspid and pulmonary atresia, interruption or coarctation of the aorta, transposition of the great vessels, hyaline membrane disease, and persistence of the fetal circulation. Differentiating TAPVC with obstruction from these other entities has improved dramatically with the advent of two-dimensional and pulse Doppler echocardiography.

Beyond the newborn period, TAPVC with or without a restrictive interatrial communication may mimic a number of congenital cardiac lesions including large ventricular septal defect, truncus arteriosus, complete atrioventricular canal defect, and single ventricle without pulmonary stenosis. Older patients with minimal or no symptoms will have findings that may suggest a large atrial septal defect, common atrium, or partial anomalous pulmonary venous connection.

Natural History

In untreated patients, the prognosis in TAPVC is determined by the presence or absence of obstruction in the extracardiac pul-

monary venous channels and the size of the interatrial communication. Infants presenting in the first few days of life with severe symptoms of pulmonary venous obstruction usually die within the first month of life. Those who survive this period often have lesser degrees of obstruction or have developed alternate pathways of pulmonary venous return.

Infants who die in the first week of life show similar gross pathologic and histologic changes.[60] The right atrium and right ventricle may appear normal, or they may show varying degrees of dilation and hypertrophy. Histologic sections of the lung reveal thickening of the alveolar walls due to massive capillary dilation and interstitial edema. Hemosiderosis is common, and lymphatic channels in the visceral pleura and interlobular septa are dilated (Fig. 69–15). The intrapulmonary arterial and venous vessels reveal increased muscularity due to marked medial hypertrophy. These findings have been observed as early as 1 day of age, which suggests a prenatal damage to the pulmonary vascular bed in patients with severe obstruction in the anomalous venous channels.[98] This dramatic muscularity has been implicated in the development of acute reversible pulmonary hypertrophy that has been observed early after repair in some infants.

Patients developing symptoms due to a restrictive interatrial communication have a prognosis not much better than that just described. Eighty percent of such infants will likely die by 1 year of age, with the majority dying in the first 6 months of life.[64,76] The cause of death is persistent severe congestive heart failure in the setting of chronic malnutrition and recurrent pulmonary infections.

In patients who are well palliated after atrial septostomy or who have a large atrial septal defect, the natural history varies. Some patients may have slight symptoms and complain only of dyspnea with exertion and exercise intolerance. Others may develop cyanosis in the second and third decade due to progressive right heart failure or pulmonary vascular disease.

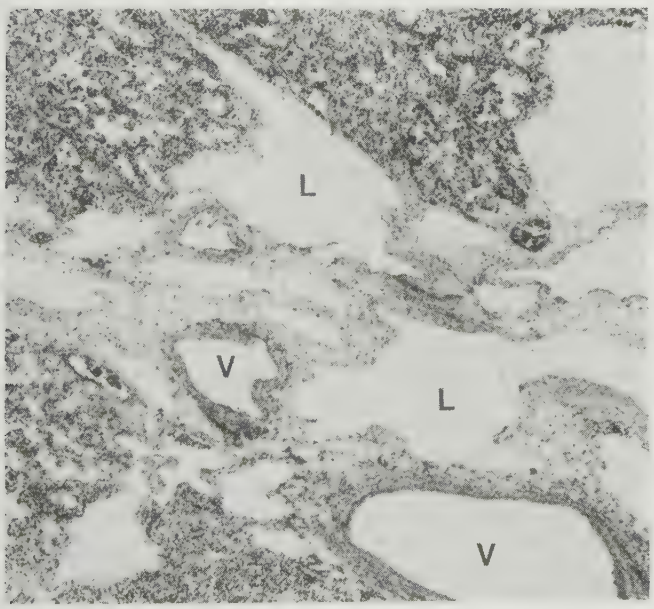

Fig. 69–15. Histologic pathology in obstructed anomalous venous connection. In a typical pulmonary septum, there are increased numbers of dilated lymphatic channels (L) as well as distended, muscularized pulmonary veins (V). Hematoxylin and eosin stain, ×40. (Courtesy of Sarah F. Johnson, M.D.)

Although pulmonary hypertension is common in patients with obstructed extracardiac anomalous venous channels or a restrictive interatrial communication, severe advanced pulmonary vascular obstructive disease (plexogenic pulmonary arteriopathy) occurs infrequently.[99,100,101] Although some investigators have disagreed on this point,[102] the postoperative hemodynamic studies support this contention.[69,71,72,103]

Treatment

In infants with TAPVC who present with marked cyanosis, respiratory distress and cardiovascular collapse in the first few days of life, severe obstruction in the extracardiac pulmonary venous channels must be assumed. Under these circumstances, cardiorespiratory and metabolic stabilization should be instituted rapidly. This may include mechanical ventilation, inotropic support and correction of acid–base or metabolic derangements. Experimental evidence[104] and one clinical report[105] suggest that prostaglandin E1 may dilate the ductus venosus and thus enhance pulmonary venous return in patients with TAPVC to the portal venous system.

After stabilization, definitive diagnostic study should be undertaken to define the connection of the anomalous pulmonary venous channel or channels. High-resolution two-dimensional echocardiography with Doppler interrogation has been used as the sole diagnostic procedure prior to emergency surgical intervention in some patients.[83,106] Precise delineation of the anomalous venous connection in patients with a mixed type of TAPVC or in those with complex associated anomalies (asplenia syndrome) may be more difficult,[85,107] and in these cases cardiac catheterization with selective angiography is advisable.

Although most investigators agree that urgent surgery is indicated in all cases of TAPVC with severe extracardiac obstruction, controversy exists in the management of those patients without severe extracardiac obstruction, most of whom present after the early newborn period. In our series of 21 patients with TAPVC without extracardiac obstruction, we performed balloon or blade/balloon atrial septostomy at the time of diagnosis followed by aggressive medical therapy and close followup.[71] Seventy-five percent of these patients were well palliated and underwent elective surgical repair in the second year of life with a mortality of 5%. The others required surgical intervention because of persistent severe congestive heart failure and failure to thrive. The morbidity and mortality observed in our patients compares favorably with recent results of surgical correction at the time of diagnosis.[103,108,109] Circumstances that may dictate an early palliative approach with later total correction include 1) some cases of mixed type TAPVC in which multiple small anastomoses between the pulmonary veins and the left atrium would be required; 2) patients with severe circulatory compromise because of a restrictive interatrial communication in whom the operative mortality would be better if repair could be delayed; and 3) infants unable to undergo cardiopulmonary bypass requiring blood prime because of parental religious convictions.[71]

Surgical Technique

The first attempt at surgical repair of this lesion was by Muller[15] in 1951; partial correction was achieved with the use of a closed

anastomosis between the left atrial appendage and the left upper pulmonary vein. In 1954, Burroughs and Kirklin[16] successfully repaired a cardiac TAPVC by means of the atrial well technique. One year later Lewis and Varco,[17] using moderate hypothermia and inflow occlusion, successfully repaired a cardiac-type TAPVC. Cooley and Ochsner[18] performed the first successful correction of TAPVC using cardiopulmonary bypass with a transatrial approach and an open anastomosis. In 1964, the posterior approach was introduced by Williams[110] and remains the procedure of choice at the Texas Heart Institute.[111] Other centers[69,112] continue to use a modification of the original transatrial approach of Cooley because of difficulties with distortion of the anastomosis that may occur when the heart is displaced from its anatomic position. In the majority of newborn and very young infants, deep hypothermia with circulatory arrest often is used to perform the repair. In older infants, normothermic cardiopulmonary bypass using cold potassium cardioplegia for myocardial protection has been used with equally good results.[71]

Surgical approaches for the specific anomalies follow:

TAPVC of the Supracardiac or Infracardiac Type. Either a right transatrial or a posterior approach is used in these circumstances (Fig. 69–16). The common pulmonary vein is mobilized, and the ascending or descending vein is ligated. Creation of a large side-to-side anastomosis between the left atrium and common pulmonary vein is then performed, often using an incision in the left atrium that runs from the left atrial appendage into the right atrium to maximize left atrial volume. The interatrial communication is then closed with pericardium or prosthetic material.

Cardiac Type TAPVC. A right atrial approach is used, and in the case of TAPVC to the right atrium, the interatrial septum is excised completely and a pericardial or prosthetic patch is sutured to close the atrial septal defect and direct all of the pulmonary venous return into the left atrium. When the pulmonary venous connection is through the coronary sinus, the partition between the coronary sinus and the right atrium is excised along with the interatrial septum. A septum is then fashioned with pericardium or prosthetic material to direct the pulmonary veins into the new left atrium (Fig. 69–17). Using this technique, the coronary sinus veins are identified and the patch is sutured behind these veins in order to direct coronary sinus return to the right atrium. Some surgeons prefer to use wide excision of the common wall between the left atrium and coronary sinus without enlarging the ASD. In this instance, the ASD and coronary sinus orifices are closed by direct suturing so that coronary venous blood returns to the left atrium. This mild desaturation is clinically inapparent and well tolerated.

Surgical Results

Operation for correction of TAPVC in newborns and young infants was associated with a high mortality during the early years of infant cardiac surgery. Mustard et al.[112] reported no survivors in attempted total correction in 1962, and Cooley and associates[113] experienced a 54% mortality up to 1966. Survival improved in the 1970s with two large centers reporting an operative mortality of 36%.[114,115] This improvement in operative survival was linked to a number of factors including: 1) earlier recognition and prompt referral; 2) complete diagnosis using cardiac catheterization and angiocardiography; 3) aggressive preoperative medical management; 4) total correction using deep hypothermia and circulatory arrest to enhance construction of a large anastomosis in a bloodless operative field; and 5) intensive postoperative management, including strict attention to fluid balance and aggressive treatment of pulmonary complications.[114]

Despite improvement in overall operative results during this period, mortality remained high in infants less than 6 months of age. This led some centers to recommend aggressive medical management (including balloon septostomy) in hopes of delaying surgery until after the first 6 months of life[92,115] in those patients without extracardiac obstruction. Other investigators found determinants of early survival to be unrelated to age per se, but rather to the anatomic type of TAPVC,[108,114,116] the presence of pulmonary hypertension related to intracardiac or extracardiac obstruction,[103,108,109,117] and the patient's clinical status at the time of presentation.[103,112,117] For these reasons, many centers have adopted the approach of urgent surgical intervention shortly after diagnosis in all patients, whether there is severe obstruction or not. Using this approach, operative mortality has ranged from 8 to 13%.[107,108,117] Most of these patients had supracardiac or cardiac TAPVC. In fact, Mazzucco, et al.[109] reported no deaths in patients with TAPVC of the supracardiac and cardiac type. These results are encouraging and have led other centers to adopt a similar approach.

Unfortunately, operative mortality in those patients with infracardiac TAPVC or in patients with complex cardiac lesions in association with TAPVC remains high, ranging from 14 to 67%.[108,109,117]

Long-term Results

The long-term outlook in patients surviving correction of TAPVC is excellent. This is reflected in reported postoperative hemodynamic and angiographic studies. Pulmonary artery pressures are found to be normal or only mildly elevated in most cases;[21,71,103,117] the elevation is usually due to an increase in the pulmonary artery wedge pressure rather than increased calculated pulmonary arteriolar resistance. The elevation in pulmonary artery wedge pressure is found commonly and is considered due to mild anastomotic obstruction. Angiographically, however, the anastomosis usually appears widely patent in these patients with rapid emptying of contrast material from the pulmonary veins, thereby suggesting this obstruction has no functional significance.[69] The abnormalities in left ventricular size and function observed preoperatively become normalized in most patients[21,72,103,118] (Fig. 69–18), and right ventricular size returns to normal as well.

Reoperation after repair of total anomalous pulmonary venous connection has been reported in up to 20% of cases. Anastomotic obstruction may occur in all types of TAPVC and has been linked to the operative approach and the surgical technique employed.[119–121] The use of continuous nonabsorbable suture material for construction of the anastomosis may be responsible for some causes of late obstruction. This has led to the recent use of a newly developed, stronger absorbable monofilament suture material (polydioxanone) for construction of the anastomosis. Although short-term results have been encouraging,[121] long-term results are not known. A more difficult problem arises when obstruction occurs proximal to the anastomotic site in the pulmonary veins themselves. This complication appears to be more common in infradiaphragmatic TAPVC[108,119,120] but has been found in other types of lesions, most commonly anomalous connection to the coronary sinus.[68,121] This obstruction is due to partial or complete obliteration of the ostia of the pulmonary veins by fibrosis similar to that lesion

Fig. 69–16. Repair of supracardiac TAPVC using the posterior approach. (Reprinted with permission from Reardon, M.J., et al.: Total anomalous pulmonary venous return: Report of 201 patients treated surgically. Texas Heart Inst. J., *12*:131, 1985.)

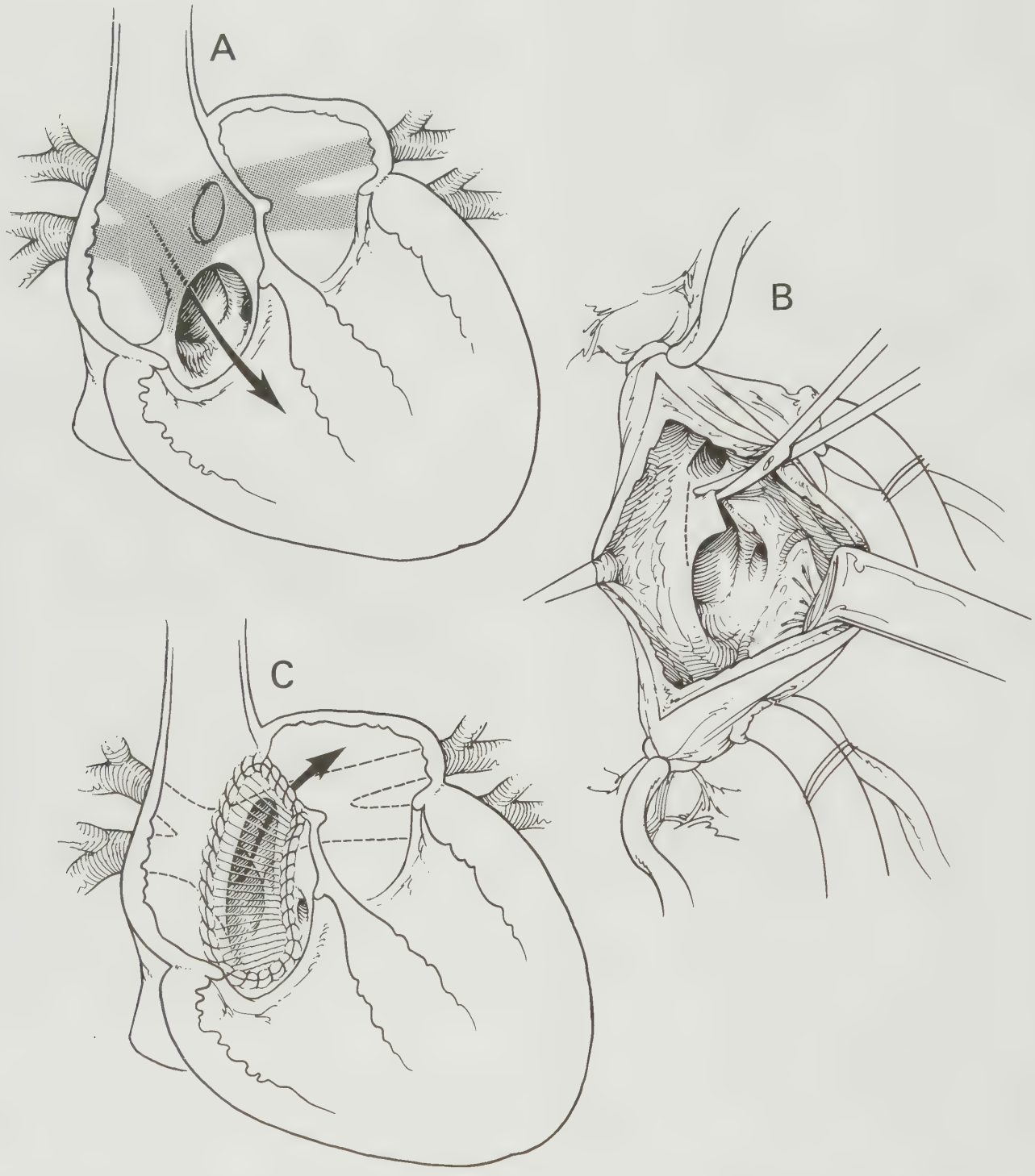

Fig. 69–17. Repair of cardiac type TAPVC to the coronary sinus. (Reprinted with permission from Reardon, M.J., et al.: Total anomalous pulmonary venous return: Report of 201 patients treated surgically. Texas Heart Inst. J., *12*:131, 1985.)

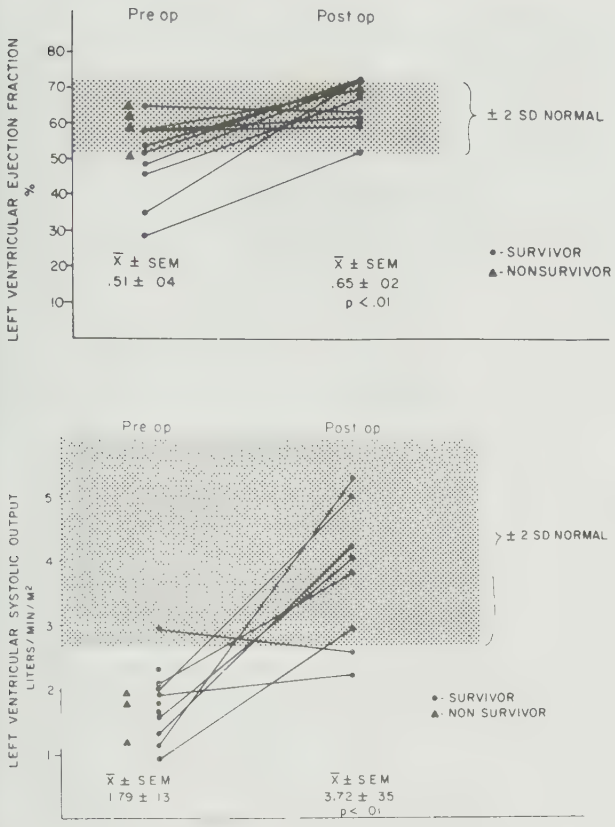

Fig. 69–18. Normalization of left ventricular ejection fraction and systolic output after repair of TAPVC. (Reprinted with permission from Hammon, J.W., Jr., et al.: Total anomalous pulmonary venous connection in infancy. J. Thorac. Cardiol. Surg., *80*:544, 1980.)

found in isolated stenosis of the pulmonary veins. Results of reoperation for this complication are uniformly poor.[108,121]

Late arrhythmias may develop in a small number of patients after operative correction of TAPVC. Atrial arrhythmias are most common and include sinus bradycardia as well as supraventricular tachycardia and atrial flutter. Ventricular arrhythmias are rare.

The Future: Prenatal Diagnosis

Recent advances in fetal echocardiography have led to the prenatal diagnosis of a number of congenital cardiac defects.[122,123] Abnormalities in pulmonary venous connection, however, have not yet been described. The difficulty with prenatal diagnosis of abnormalities in pulmonary venous connection is likely due to a number of factors including the relative infrequency of abnormalities in pulmonary venous connection in the spectrum of congenital heart disease, the lack of a "genetic predisposition" for the development of this anomaly, and normal fetal blood flow patterns that mask abnormalities in pulmonary venous anatomy and function. The prenatal detection of infradiaphragmatic TAPVC would be expected to increase the chances of survival if surgery were performed shortly after delivery prior to the development of severe symptoms. Recent work in the area of intrauterine cardiothoracic surgery in the fetal lamb[124] suggests that prenatal correction of congenital cardiac defects, including abnormalities of pulmonary venous connection, may be feasible in the near future.

STENOSIS OF THE INDIVIDUAL PULMONARY VEINS

Stenosis of one or more of the individual pulmonary veins in the absence of anomalous pulmonary venous connection is rare. Reye[125] reported in 1951 the autopsy findings on an 8-year-old patient who died with severe stenosis of three pulmonary veins and atresia of the fourth. Bini et al.[126] reviewed 38 cases reported up to 1984 and added 10 of their own. In Bini et al.'s 10 cases, all major pulmonary veins were obstructed; however, the type of obstruction and the severity of involvement was unique in each patient illustrating the wide spectrum of disease that may be encountered.

Embryology and Pathology

Edwards[127] has proposed that stenosis of the individual pulmonary veins is due to abnormal incorporation of the common pulmonary vein into the left atrium in the later stages of cardiac embryogenesis. This thesis is supported by the observations of Shone, et al.[128] and are enumerated as follows: 1) there is a frequent association with other congenital cardiac anomalies; 2) most patients become symptomatic in the first few years of life; 3) there is a similarity in the histopathologic lesion that occurs in normally inserting pulmonary veins and in those veins that insert into structures other than the left atrium (TAPVC); and 4) the absence of the active inflammation in or around the involved segments of vein.

The pathologic anatomy varies widely in both the number of pulmonary veins involved and in the degree of involvement. Three distinct types of pulmonary vein stenosis have been described (Fig. 69–19): 1) long-segment hypoplasia of a pulmonary vein that may extend into the lung parenchyma; 2) a discrete "diaphragm" occurring in the extrapulmonary veins;[129] or 3) focal or diffuse intimal fibrosis localized to the pulmonary vein ostia or extending some distance into the pulmonary veins. Diffuse, long-segment hypoplasia of the entire extraparenchymal vein is often found in patients with severe pulmonary artery stenosis or atresia and has been described in the hypoplastic left heart syndrome.[34] Discrete lo-

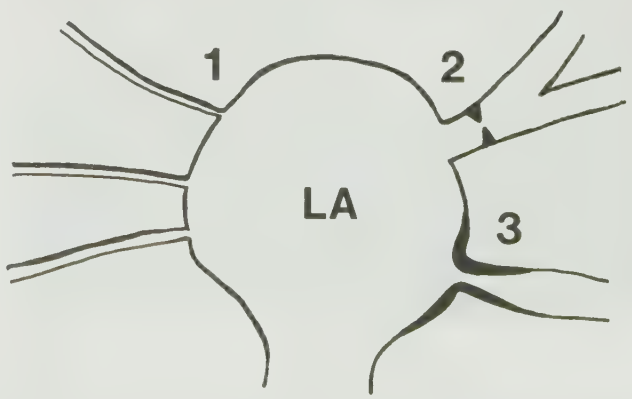

Fig. 69–19. Types of pulmonary vein stenosis. 1) Long segment hypoplasia. 2) Discrete diaphragm. 3) Focal intimal fibrosis.

calized obstruction at the veno–atrial junction is the most common pathologic process, and the gross and histologic findings are similar in all reported cases (Fig. 69–20).[126–128] There is nonspecific intimal thickening due to elastic and fibrous tissue proliferation with different degrees of irregularity of the media. The thickening is most prominent at the veno–atrial junction, but may extend some distance into the extraparenchymal pulmonary vein. All three types of obstructive lesions may occur in the same patient, although one is usually predominant.[126]

Associated cardiac defects occur in over 50% of patients with stenosis of the pulmonary veins, the most common being atrial and ventricular septal defects.[130] The pathologic cardiac findings observed in patients with pulmonary vein stenosis are similar to those found in other cardiac disease producing elevation of pulmonary venous pressure. Dilation of the intrapulmonary lymphatic channels and interstitial edema are present, and variable degrees of medial hypertrophy of the pulmonary veins occur. The pulmonary artery usually is dilated and thick-walled, and there is right ventricular and right atrial hypertrophy.

Fig. 69–20. Gross pathologic findings in pulmonary vein stenosis. Nonspecific intimal thickening due to elastic and fibrous tissue proliferation involving the left atrial endocardium extending into the pulmonary vein ostia. Probe 1 mm in diameter placed in left upper pulmonary vein. (Courtesy of Billy M. Abla.)

Clinical Features

Most patients present in the first few years of life with a long history of respiratory symptoms, including persistent tachypnea and recurrent pneumonia. There is often failure to thrive of a chronic nature interspersed with acute episodes of life-threatening pulmonary edema and right-sided cardiac failure. Hemoptysis may be a prominent symptom, especially in older children. Cyanosis may occur in patients with severe pulmonary edema, or in those with right-to-left intracardiac shunt. Physical examination reveals signs of pulmonary hypertension including a right ventricular lift, a loud pulmonary component of the second heart sound, and a nonspecific systolic murmur over the base. In addition, the murmurs of tricuspid and pulmonary insufficiency often are detected. Electrocardiography demonstrates right ventricular hypertrophy as well as right atrial enlargement in most cases.

Diagnostic Studies

Radiologic Features

The heart may be normal-sized or may demonstrate features of right ventricular hypertrophy and/or dilation, right atrial enlargement, and dilatation of the pulmonary artery. The characteristic reticular markings of pulmonary venous obstruction usually are present and may be unilateral or localized to a single pulmonary segment (Fig. 69–21). In addition, shift of the cardiomediastinal silhouette to the side of major involvement often is observed due to diminished arterial perfusion of the affected lung, leading to diminished pulmonary volume.[131] There may be increased arterial vascular markings in unaffected lung segments as a result of re-

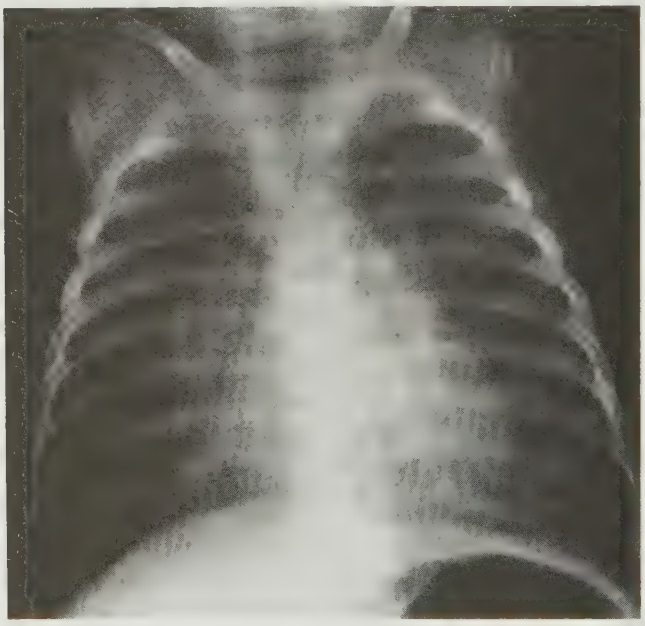

Fig. 69–21. Chest radiograph in pulmonary vein stenosis. There is mild hyperinflation of both lungs and mild cardiomegaly with straightening of the left heart border suggestive of right ventricular enlargement. The central pulmonary vascularity is indistinct due to perihilar congestion. Prominent pulmonary venous markings are apparent and most notable in the left lower lobe.

distribution of pulmonary blood flow away from the obstructed lobes.

Radionuclide Studies

In cases of predominantly unilateral pulmonary vein stenosis or atresia, there is a marked disparity in perfusion as demonstrated by radionuclide perfusion lung scans.[133] Radionuclide ventilation studies also may be abnormal showing underventilation of the affected lung due to decreased lung volume and poor compliance.[134]

Echocardiographic Features

The characteristic echocardiographic findings are those of severe pulmonary hypertension and include dilatation of the pulmonary artery, right ventricle, and right atrium and right ventricular hypertrophy. Doppler echocardiography demonstrates evidence of pulmonary hypertension and may reveal pulmonary and tricuspid valve insufficiency. Careful examination of the left heart structures should be performed to rule out other causes of pulmonary venous obstruction, including valve or supravalve mitral stenosis and cor triatriatum. Recently, pulsed Doppler sampling at the pulmonary vein/left atrial junction was used by Smallhorn[135] to detect pulmonary vein stenosis prior to cardiac catheterization. He was able to demonstrate a disturbed, high-velocity venous flow pattern at the ostia of the right upper pulmonary vein that was different from the normal pulmonary vein flow profile.

Cardiac Catheterization

Cardiac catheterization and cineangiography usually are diagnostic in this lesion, although the findings may be subtle and usually require a high index of suspicion. Suprasystemic pulmonary hypertension often is observed with elevation of pulmonary capillary wedge pressure ipsilateral to the side of obstructed pulmonary venous drainage.

In the case of unilateral obstruction, pulmonary arteriography reveals delayed circulation on the side of stenosis and diversion of blood away from the affected pulmonary artery, producing the "dead tree" appearance first described by Edwards.[127] Reversal of flow in diastole in the pulmonary artery of the ipsilateral lung may be observed as well. If precise anatomic details of the pulmonary venous anatomy are not obtained by pulmonary artery cineangiograms, selective right and left pulmonary artery wedge injections may be helpful.[126] Direct injection into the affected pulmonary vein has also been reported, although often the stenosis is so severe that even a small caliber catheter cannot be manipulated into the obstructed vein.

Differential Diagnosis

The differential diagnosis in patients with clinical findings of pulmonary hypertension include left heart obstructive lesions (mitral stenosis, cor triatriatum), idiopathic pulmonary hypertension, pulmonary veno–occlusive disease, constrictive pericarditis or mediastinitis, pulmonary venous phlebitis due to tuberculosis, or invasion of the pulmonary veins by tumor tissue.[128]

Prognosis and Therapy

Unless only a single pulmonary vein is involved, the prognosis in patients with this disease is grim. Most patients succumb to progressive right heart failure, recurrent hemoptysis, or pulmonary infection.

Attempts at correction of this cardiac defect have been unsatisfactory. Dilatation of the pulmonary veins by balloon catheter has been attempted with reports of short-term success; however, stenosis always recurs.[136,137] Surgical treatment of this lesion has been equally disappointing.[126,130,136] Techniques that have been used in the repair include simple excision of an obstructing diaphragm,[138] excision and venoplasty using pericardium[129] or prosthetic material,[126] simple excision and reimplantation of the pulmonary vein into the left atrium,[130] and creation of autologous atrial flaps to widen the venoatrial junction.[139] Although satisfactory relief of pulmonary vein obstruction has been documented early postoperatively by a decrease in pulmonary pressure and improvement in the angiographic appearance, re-stenosis has recurred in almost all cases reported. In the few reported cases in which re-stenosis did not recur early, the patients were older[138] or had significant pulmonary venous obstruction confined to only one lung.[129,139]

The poor prognosis in most patients with stenosis of the individual pulmonary veins suggests that alternative therapeutic modalities be investigated. One option presently being investigated in the animal model is the placement of an expandable intravascular stent at the site of venous obstruction. These stents appear to be well tolerated in short-term studies without evidence of disruption of the vessel wall or thrombosis.[140] Clinical trials of this therapeutic modality are forthcoming. An alternative approach would be that of heart/lung transplantation as has been used in patients with primary pulmonary hypertension.

ATRESIA OF THE COMMON PULMONARY VEIN

Atresia of the common pulmonary vein occurs when the individual pulmonary veins connect to a pulmonary venous confluence that ends blindly behind the left atrium. Under these circumstances, severe obstruction to pulmonary blood flow occurs shortly after birth leading to marked hypoxemia, acidemia, and in most cases, death in the first days or weeks of life. Lucas et al.[141] first coined the term *atresia of the common pulmonary vein* to describe the pathologic findings in three infants who died with this anomaly. Since that original description in 1962, 17 cases have been reported in the literature including the report by Khonsari et al.[142] in which the first successful surgical correction was achieved.

Embryology and Anatomy

The embryologic abnormality that has been postulated to occur in these infants is obliteration of the connection between the common pulmonary vein and left atrium after obliteration of the primitive pulmonary to systemic venous channels. This theory is supported by the findings of an atretic fibrous strand of tissue extending from one of the pulmonary veins to the right or left atrium,[141] or connecting the common pulmonary vein to a systemic vein.[143] Patency of the ductus arteriosus has been found in all patients, although other significant cardiac defects are uncommon.

The lungs are characteristically firm and congested, with prominent lobules outlined by edematous interlobular tissue and dilated lymphatic channels.[141] Microscopic examination reveals medial hypertrophy of both small pulmonary arteries and pulmonary veins reflecting longstanding prenatal pulmonary venous obstruction.

The alveoli may contain red blood cells and iron-containing macrophages.[141]

Hemodynamics

The altered hemodynamics observed are those of severe obstruction to pulmonary venous return. Pulmonary blood flow is markedly diminished and is diverted away from the pulmonary circuit through right-to-left shunting through the foramen ovale and ductus arteriosus. Profound hypoxemia ensues, leading to metabolic acidosis that is unresponsive to medical therapy. Although large channels for egress of pulmonary blood do not exist, small anastomoses between the bronchopulmonary veins and the systemic venous system account for some infants' survival into the second or third week of life.[141]

Clinical Features

Infants are usually born at term after an uncomplicated pregnancy and delivery. Tachypnea and cyanosis appear within 12 hours of age in all patients and is unresponsive to oxygen administration. Physical examination reveals normal to slightly decreased peripheral pulses, a prominent right ventricular impulse without thrills, and usually a soft systolic ejection murmur of Grade I to II along the left upper sternal border. The electrocardiogram may be normal, or it may show signs of right ventricular hypertrophy.

The chest roentgenogram is usually helpful and demonstrates signs of severe pulmonary venous obstruction. The heart size is normal, and the pulmonary vascular markings demonstrate a diffuse reticular pattern and pulmonary edema characteristic of obstruction to pulmonary venous return.

Echocardiography

Echocardiographic findings in atresia of the common pulmonary vein have been reported rarely. One would expect to observe signs of pulmonary hypertension and persistence of the fetal circulatory patterns, including contrast echocardiographic or Doppler evidence of right-to-left shunting at the foramen ovale or ductus arteriosus. In addition, the common pulmonary venous chamber may be visualized behind the left atrium without a connection to the heart or a systemic vein. Total anomalous pulmonary venous connection with obstruction and persistence of the fetal circulation may be difficult to differentiate from this anomaly if the blind common pulmonary venous chamber is not observed.

Cardiac Catheterization

Cardiac catheterization reveals pulmonary hypertension of a severe degree in all cases. Pulmonary angiography demonstrates a large patent ductus arteriosus with predominant right to left shunting and markedly prolonged filling and clearing of the pulmonary vascular bed with contrast material. No opacification of the left atrium is observed and only rarely is the pulmonary venous confluence visualized.[144] Oximetric studies demonstrate equally low oxygen saturations in all chambers of the heart. When there is a step up in oxygenation, this occurs between the superior vena cava and the right atrium and is due to blood returning from the bronchopulmonary collaterals by the azygous system of veins.[145,146]

Management

Early recognition of signs and symptoms of pulmonary venous obstruction is critical if one is to affect the high mortality associated with this cardiac defect. Although cardiac catheterization and angiocardiography have been the diagnostic procedure of choice in previous reports, high-resolution two-dimensional echocardiography with Doppler capabilities may replace this modality in the extremely ill, moribund infant. Aggressive preoperative medical management including early mechanical ventilation and the judicious use of sodium bicarbonate for metabolic acidosis is advocated. In addition, prostaglandin E1 may be helpful if signs of constriction of the ductus arteriosus and poor systemic perfusion are present.

An attempt at surgical correction should be undertaken as soon as the diagnosis is established. Khonsari et al.[142] reported the first infant to survive operation in 1982. Using deep hypothermia and limited bypass supplemented by cold cardioplegic arrest, the ductus arteriosus was first identified and ligated. An anastomosis was performed between the posterior aspect of the left atrium and the common pulmonary venous channel, and the foramen ovale was closed. The postoperative course was uneventful, and the infant was discharged on the seventh postoperative day.

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CHAPTER 70

Transposition Physiology

J Timothy Bricker

Transposition physiology is defined as the situation of a systemic and a pulmonary circulation that are connected in parallel rather than in series. Mixing between the systemic and pulmonary circulations is essential for survival. In transposition physiology, the mixing between the parallel circulations is equal to the left-to-right or right-to-left shunt. The right-to-left and left-to-right shunt must be equal in transposition, or the blood volume would end up entirely in the systemic or in the pulmonary circulation.

Oxygenation of the systemic side is reflected in the right-to-left shunt between the two circulations. Thus, the Q_{ES} (effective systemic output) will be equal to the right-to-left shunt. In the same respect, delivery of deoxygenated blood to the pulmonary circulation (Q_{EP}, or effective pulmonary blood flow) is equal to the left-to-right shunt. So, in transposition physiology, it may be seen that mixing is equal to effective pulmonary blood flow, which is equal to effective cardiac output, which is equal to right-to-left shunt, which is equal to left-to-right shunt. This is a fairly simple concept but is regularly a source of confusion for the neophyte performing cardiac catheterization laboratory calculations (see Chapter 54).

Pulmonary blood flow with transposition physiology is unrelated to effective pulmonary blood flow or to oxygenation of the patient. A cyanotic newborn showing normal or increased pulmonary vascular markings on chest radiograph will often be a clue to the neonate with transposition physiology.

CLINICAL SETTING OF TRANSPOSITION PHYSIOLOGY

It must be emphasized that transposition physiology may occur in conjunction with a number of different defects other than the typical d-transposition of the great arteries. Many patients with double outlet right ventricle, single ventricle, and ventricular inversion without transposition (''isolated ventricular inversion'') will have transposition physiology. In the same respect, a patient with classic d-TGA relationship of the great arteries may not have transposition physiology.

One example of this might be a patient with tricuspid atresia and transposition having the physiology of a left-to-right shunt. Another example is that of a patient having a single ventricle with severe pulmonary stenosis, d-TGA relation of the great vessels, and the physiology of a right-to-left shunt. Patients who have ventricular inversion with transposition and without an interatrial or an interventricular communication may have normal physiology—the classic ''congenitally corrected'' transposition.

Although morphologists may argue about the anatomic definitions of transposition, being alert about the physiologic definition of ''transposition physiology'' can help prevent blunders in the catheterization laboratory. We continue to see double outlet right ventricle or isolated ventricular inversion cases with transposition physiology and inadequate mixing who are referred after a cardiac catheterization in which balloon atrial septostomy was omitted because it was not a classical d-TGA. A convenient rule of thumb in the catheterization laboratory is that if a newborn has a higher oxygen saturation in the pulmonary artery than in the aorta, it is either anomalous pulmonary venous return or transposition physiology.

The location of pulmonary venous return should be identified if there is a question of whether the patient has transposition physiology. If transposition physiology is confirmed in a cyanotic

Table 70–1. Indications for Creation of an Atrial Septal Defect in the Catheterization Laboratory

Indication	*Comment*
Transposition physiology	May not be best to perform septostomy if arterial switch is planned for the immediate future and if adequate mixing between the circulations can be assured.
Left atrial hypertension from obstructed egress	An example of this would be a single ventricle with mitral atresia and a restrictive foramen ovale.
Tricuspid atresia with a restrictive atrial septal defect	The effective cardiac output in tricuspid atresia depends upon and is equal to the right-to-left flow at the level of the foramen ovale. Right-sided volume overload (e.g., hepatomegaly) with low cardiac output will be found with a restriction to flow at the atrial level.
Total anomalous pulmonary venous return with obstruction at the atrial level	Extracardiac obstruction of pulmonary venous return is usually recognized but an intracardiac obstruction of anomalous return to the left heart at the atrial septal level is frequently overlooked. Improvement in cardiac output and a decrease in pulmonary edema follow creation of an atrial defect during catheterization in these patients.
Severe right heart failure with pulmonary hypertension	Some pulmonary hypertension patients with intact atrial and ventricular septae have incapacitating symptoms of right heart failure. Creation of an atrial communication will relieve right-sided symptoms at the expense of increased cyanosis.

baby, one should proceed with a balloon septostomy unless an arterial switch is planned for the near future and adequate mixing can be assured in the interim. Transposition physiology is not the only indication for creation of an atrial septal defect (Table 70–1). This concept is a source of occasional confusion when one is attempting to determine whether to perform a septostomy.

ADEQUACY OF MIXING IN TRANSPOSITION PHYSIOLOGY

The mixing between the pulmonary and systemic circulations in transposition physiology may be at the level of the atriae, ventricles, or great arteries. For example, an infant with typical d-TGA and a ventricular septal defect may be well saturated. In general, creation of an atrial defect in such a patient is reasonable because of the possibility of development of a restrictive interventricular communication. Some of these patients may have better mixing and a higher saturation with septostomy and, furthermore, they may improve with a drop in left atrial pressure from septostomy. Mixing at the great vessel level may occur in the patient with transposition physiology and a patent ductus arteriosus. Prostaglandin E_1 therapy to open the ductus arteriosus may serve to improve mixing at the great vessel level. This therapy can be useful for stabilization prior to transport, to cardiac catheterization, and to balloon atrial septostomy.

One of the important problems for the baby with transposition physiology is inadequate mixing. One of the causes of inadequate mixing after septostomy is an inadequate septostomy. An adequate atrial septal defect should be confirmed by angiogram or echocardiogram performed in the catheterization laboratory before the procedure is concluded. Volume loading and an increase in oxygen-carrying capacity by an infusion of packed red blood cells will improve oxygenation in the patient with poor atrial mixing after balloon septostomy. A complicated relationship of the diastolic impedance of the atriae and ventricles is involved in the adequacy of atrial mixing. Anecdotal observations and preliminary clinical studies suggest that the use of prostaglandin E_1 infusions with transposition physiology may increase the problem of poor mixing after balloon atrial septostomy.

Defining poor mixing in transposition physiology is difficult. The apparent increase in poor mixing may be in part due to the increased surveillance with blood gases, transcutaneous oxygen tension measurement, and photometric monitoring of oxygen saturation that is characteristic of current neonatal intensive care practice. Hypoxemia without acidemia in the baby with transposition and an adequate interatrial communication usually gradually improves and is tolerated in the interim. Inadequate mixing with associated acidosis due to hypoxemia is a reason for early repair by Senning, Mustard, or arterial switch technique. Complications of hypoxemia may occur with time in patients with transposition as in patients with right-to-left shunt discussed in Chapter 62. Greater detail about the physiology of transposition, particularly as it relates to the timing and type of surgical intervention, will follow in Chapter 71.

CHAPTER 71

Transposition of the Great Arteries

William H Neches
Sang C Park
Jose A Ettedgui

Transposition of the great arteries, or complete transposition, is a common form of cardiac anomaly and is found in about 5% of all patients with congenital heart disease.[1] The word transposition refers to the discordant ventriculoarterial connection of the great arteries whereby the aorta originates from the morphologic right ventricle and the pulmonary artery originates from the morphologic left ventricle. The consequence of this anatomic arrangement is that nonoxygenated systemic venous blood returning to the heart passes through the right atrium and right ventricle and is ejected into the aorta. Similarly, oxygenated pulmonary venous blood reaches the left side of the heart and is returned to the pulmonary artery.

The clinical situation that results from this cardiac anomaly is characterized by severe and life-threatening hypoxemia early in life. Although Baillie described the first recorded case of transposition of the great arteries almost two centuries ago, in 1797, it remained little more than an anatomic curiosity until the era of cardiac catheterization and cardiac surgery.[2] Prior to this, over 90% of patients with transposition died in infancy and transposition of the great arteries was one of the most common causes of death from congenital heart disease in the first year of life.[3–6]

In recent years, advancements in cardiac catheterization and cardiovascular surgery have transformed the devastating natural history of this anomaly. Blalock and Hanlon developed surgical atrial septectomy in 1950, which resulted in improved survival for infants with transposition.[7] Although the first physiologically corrective atrial baffle procedure was described by Senning toward the end of that decade, the results were unacceptably poor and it was therefore abandoned.[8] A few years later, in 1964, the introduction of another atrial redirection procedure by Mustard revolutionized the approach toward the surgical management of the patient with transposition.[9] The introduction of balloon atrial septostomy by Rashkind and Miller in 1966 was the single most important factor to influence the survival of the infant with transposition.[10] This procedure allowed successful palliation of the young infant with transposition of the great arteries without operation and with low risk. Thus, by the end of the 1960s the availability of balloon atrial septostomy and widespread success with the Mustard procedure resulted in an aggressive approach to the management of the newborn and small infant with transposition of the great arteries.

In recent years, along with the advances in medical and surgical management of patients with this disorder including the arterial switch operation, great strides have also been made in angiocardiography and echocardiography. Although it is now possible to describe precisely the anatomic variations of transposition of the great arteries in a living patient, there is still considerable discussion as to how to describe and classify patients with transposition of the great arteries. Thus, prior to a discussion of the clinical features, diagnosis, or management of patients with this disorder, it seems appropriate to review the anatomic particulars of this abnormality.

ANATOMIC CONSIDERATIONS

Basic Pathologic Anatomy

There appears to be general agreement that transposition of the

great arteries refers to the clinical situation produced by ventriculoarterial discordance in which the aorta and pulmonary artery arise from the wrong ventricles. Unfortunately, in the past, some investigators have described transposition of the great arteries not only as an abnormal ventriculoarterial connection but also in terms of the spatial relationships of the great arteries or on the basis of terminology that has been derived from embryologic hypotheses. These systems have led to confusion in classification and are quite difficult to understand in the presence of the various positioning abnormalities of the cardiac structures within the thorax such as rotational abnormalities, situs inversus, or situs ambiguous. In this chapter, the segmental description of the pathologic anatomy will be employed. For those interested in a more detailed description of the various methods of classification of transposition, references by Van Praagh et al.,[11–13] Van Mierop et al.,[14,15] and Shinebourne et al.[16] can be consulted. This chapter will deal with transposition of the great arteries as a major abnormality itself. Those situations that describe transposition in association with other major intracardiac anomalies such as atrioventricular discordance (corrected transposition), atrioventricular valve atresia, double inlet or single ventricle, or atrial isomerism syndromes are described in other chapters in this book.

The description of the pathologic anatomy of the heart in transposition of the great arteries will characterize the deviations found from various features of the normal heart. It is therefore appropriate to describe these normal characteristics. In the description of the various junctions of the heart, three important features must be distinguished: 1) connections, 2) morphology, and 3) relationships.

Situs solitus is normally present. The right atrium has its various distinguishing characteristics and is connected via a tricuspid valve to a coarsely trabeculated morphologically right ventricle. The tricuspid valve has its usual attachments to the interventricular septum. On the left side of the heart, the smooth-walled, normal-appearing left atrium connects via a mitral valve into a finely trabeculated, morphologically left ventricle, with multiple criss-crossing trabeculations. The left ventricle has a smooth interventricular septal surface with atrioventricular valve attachments away from the septum. There is thus normal intraventricular anatomy and concordant atrioventricular connection. In the heart with transposition these structures have the same characteristics. The conduction system is also normal as are the locations of the sinoatrial and atrioventricular nodes. The distinguishing features lie in the description of the ventriculoarterial junction.

In the normal heart with concordant ventriculoarterial connection, there is a subpulmonary infundibulum. The pulmonary valve is exclusively supported by muscle and there is thus no fibrous continuity between the pulmonary valve and the tricuspid valve. In the normal right ventricle, the muscle tissue that separates these two valves is the crista supraventricularis. On the left side of the heart the aorta is wedged between the mitral valve and the interventricular septum. Unlike the right ventricle, the left ventricle has no muscle tissue separating the mitral valve and the aortic valve. There is fibrous continuity between these two valves and absence of a subaortic infundibulum. Last, the two great vessels normally course in a spiral relationship as they leave the heart. As the pulmonary artery arises from the right ventricle, it ascends in a leftward direction. The pulmonary valve is generally located anterior and to the left of the aortic valve. The aorta arises from the left ventricle in the middle of the heart and ascends toward the right.

Upon external inspection of the heart with transposition of the great arteries, it is immediately apparent that there is an abnormal relationship between the great arteries (Fig. 71–1). The aorta is usually, but not always, anterior and right-sided relative to the pulmonary artery. The arterial trunks ascend in parallel fashion, rather than in a spiral, as is present in the normal heart. The atria and ventricles have their normal external morphologic characteristics and their usual relationships in either the situs solitus or situs inversus positions.

Examination of the ventriculoarterial connection demonstrates the aorta arising from the right ventricle and the pulmonary artery arising from the left ventricle. In the right ventricle there is a muscular infundibulum separating the aortic valve from the tricuspid valve, while on the left, the pulmonary artery arises from the left ventricle and there is fibrous continuity between the leaflets of the pulmonary valve and the mitral valve.

Coronary Arteries

In the normal heart, the coronary arteries arise from the two sinuses of the aortic valve, which face the pulmonary artery. The noncoronary sinus faces posteriorly and somewhat rightward. In transposition, the aorta is positioned anteriorly and generally to the right. The coronary arteries still arise from the two aortic valve sinuses that face the pulmonary artery.[17] The noncoronary sinus generally faces anteriorly and to the right. There are many variations of aortic position in hearts with ventriculoarterial discordance. However, regardless of the position of the aorta in relationship to the pulmonary artery the coronary arteries consistently arise from one or both of the aortic valve sinuses that face the pulmonary artery. This results in a relatively small distance between the origin of the coronary arteries on the aorta and the wall of vessels and the pulmonary artery, and this should facilitate

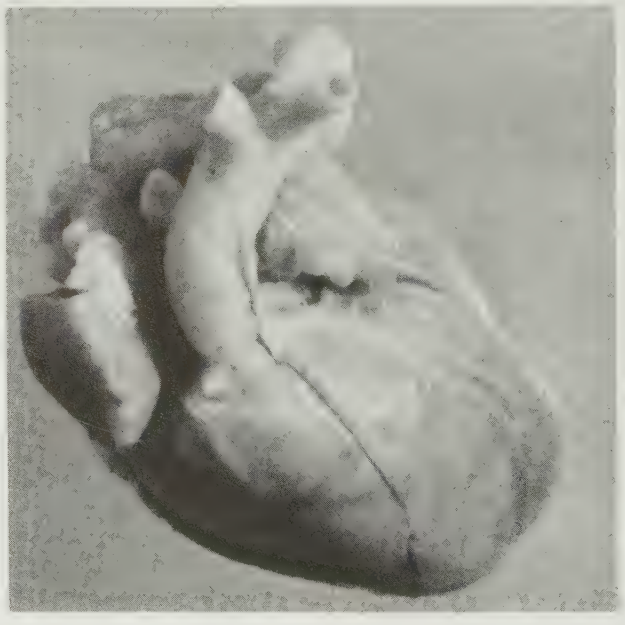

Fig. 71–1. The external appearance of a heart with transposition of the great arteries.

transplantation of the coronaries from the aorta to the pulmonary artery if an arterial switch procedure is performed.

The sinus node artery is of considerable importance in transposition of the great arteries.[18,19] This vessel arises from the right coronary artery and generally runs in the anterior interatrial groove. If it courses within the atrial myocardium, this exposes it to damage during a Blalock-Hanlon atrial septectomy or at open-heart surgery when the surgeon excises the interatrial septum while performing a Mustard procedure. The sinus node artery may also course inside the wall of the right atrial appendage until it reaches the sinoatrial node. In other cases, the sinus node artery may arise from the circumflex coronary artery especially when the circumflex runs behind the pulmonary artery. When the sinus node artery passes across the lateral aspect of the right atrium it is at risk during an atriotomy.

Major Complicating Lesions

Ventricular Septal Defect

As in the heart with normal ventriculoarterial connection, ventricular septal defects may be of varying sizes and may occur in any position in the interventricular septum (Fig. 71–2). The typical defect in transposition of the great arteries occurs in the outlet septum and may be entirely muscular or extend into the membranous septum as well.[20] In these hearts, there is most often a malalignment of the outlet septum that is deviated rightward relative to the remainder of the ventricular septum.[21] As a result, the pulmonary valve and pulmonary artery may override the ventricular septum in varying degree. This overriding leads to a spectrum of cardiac malformations that range between discordant ventriculoarterial connections with slight override of the pulmonary artery, to the Taussig-Bing malformation (double outlet right ventricle with subpulmonary ventricular septal defect). This latter anomaly, though anatomically part of the complex of double outlet right ventricle, physiologically is in the category with transposition. Although the pulmonary artery arises from the right ventricle along with the aorta, the subpulmonic location of the ventricular septal defect results in highly oxygenated pulmonary venous blood passing into the pulmonary artery just as it does in transposition. In some cases with transposition and ventricular septal defect or in the Taussig-Bing malformation, significant deviation of the outlet septum into the right ventricular outflow tract may result in subaortic outflow obstruction.[22,23] This may result in reduced flow into the aorta during fetal life and may be the cause for the high incidence of coarctation of the aorta that is found in conjunction with this anomaly.[24] Other types of ventricular septal defects such as those located in the membranous septum or muscular trabecular defects (single or multiple) may be present in patients with transposition of the great arteries.[20]

The major difference between these defects in transposition as compared to the heart with concordant ventriculoarterial connection lies in the surgical approach. If an atrial baffle procedure is performed, the right ventricle remains the systemic ventricle after repair. Thus, a ventricular septal defect must be approached via the right atrium and tricuspid valve rather than through a ventriculotomy.[25,26] In general, this is not a problem with defects in the membranous septum or with isolated muscular trabecular defects. On the other hand, multiple muscular defects are more difficult to repair since direct vision is more limited without the availability

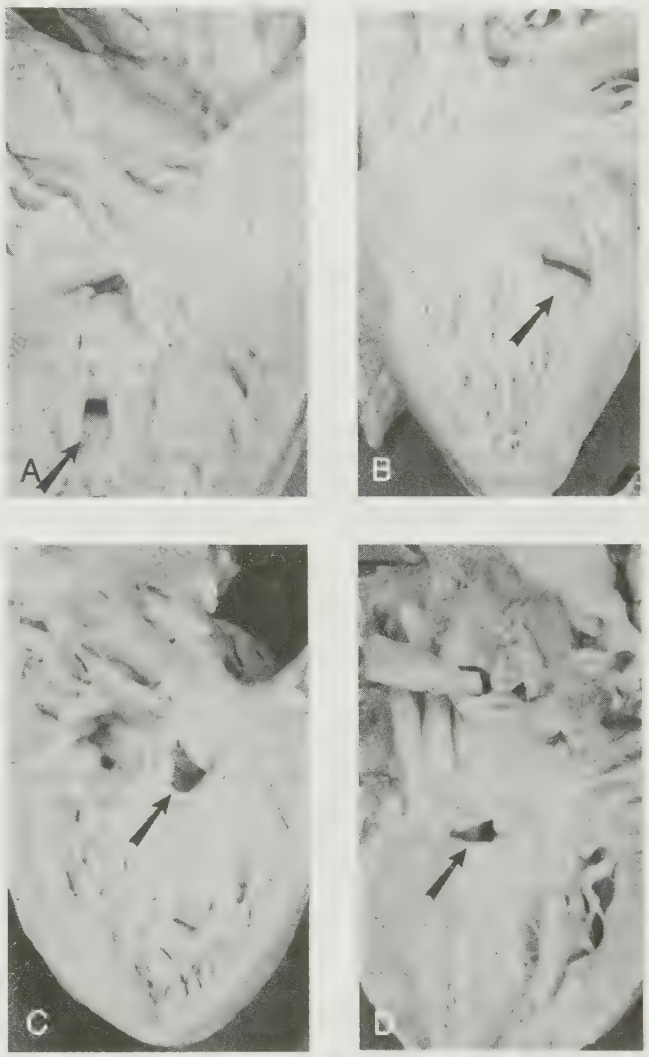

Fig. 71–2. Ventricular septal defects in transposition of the great arteries (arrows). (A) Inlet defect, left ventricular aspect. (B) Inlet defect, right ventricular aspect. (C) Malalignment defect, right ventricular aspect. (D) Malalignment defect, left ventricular aspect.

of a ventriculotomy. Fortunately, these latter defects are much less common in association with transposition. Inlet ventricular septal defects are of major importance in patients with transposition of the great arteries. These may be purely muscular or may be membranous with muscular extension.[20] The major significance of these defects in patients with transposition is due to the fact that they lie underneath the septal leaflet of the tricuspid valve. Again, if an atrial baffle repair is contemplated, surgical access must be via the right atrium rather than through a ventriculotomy. The tricuspid valve overlies the defect and must be retracted in order to perform the repair adequately. It is possible that injury to the valve during repair may be responsible for the tricuspid regurgitation seen in some patients who have undergone closure of inlet ventricular septal defects at the time of an atrial baffle operation.

In most hearts with transposition and ventricular septal defect, the conduction tissue is also located in its usual position.[27,28] With the more common type of membranous or muscular outlet defects the conduction tissue lies on the left ventricular side of the septum

and courses around the posterior and caudal margins of the defect. In contrast, when a purely muscular inlet defect is present, it is likely that the conduction tissue will run in the muscular ridge between the cephalad rim of the defect and the membranous septum.[29] When this type of defect is present, the surgeon must take great care when placing sutures in the cephalad portion of the defect rather than caudally as is usually the case.

Pulmonary Stenosis

Left ventricular outflow tract obstruction can be demonstrated in over 30% of patients with transposition of the great arteries.[30–32] In patients with an intact interventricular septum, a dynamic form of left ventricular outflow tract obstruction is most common. As a result of the pressure difference between the systemic right ventricle and subpulmonary left ventricle, there is usually a distinct leftward bulge in the upper portion of the interventricular septum into the left ventricular outflow tract. This dynamic obstruction occurs during systole and is readily appreciated both angiographically and by echocardiography.[33,34] In many cases this results in a relatively small (20 to 30 mm Hg) peak systolic pressure gradient between the left ventricle and pulmonary artery. In some cases, especially those with greater left ventricular outflow tract gradients, a discrete fibromuscular shelf may be present on the septal surface of the outflow tract and may even extend laterally onto the mitral valve.[31] This shelf most commonly represents a hemodynamic change in the septal surface secondary to the obstruction resulting from the protrusion of the interventricular septum into the left ventricular outflow tract. Valvar pulmonary stenosis is a possible but infrequent cause of left ventricular outflow obstruction.[30,35] If present, it is usually in association with the dynamic form of obstruction and oftentimes is the less severe of the two. Other forms of subpulmonic obstruction include anomalous attachments of atrioventricular valve tension apparatus and fibrous tissue tags.[35]

An important form of subpulmonic obstruction in transposition of the great arteries is the form that occurs in the presence of a ventricular septal defect. These hearts have a more extensive type of stenosis consisting of a narrow fibromuscular tunnel in the left ventricular outflow tract.[36] In the discussion regarding ventricular septal defect, the form of transposition of the great arteries and ventricular septal defect was described in which the pulmonary valve overrides the interventricular septum. In some of these cases the outlet septum is sufficiently deviated into the right ventricle so as to produce right ventricular outflow tract obstruction (subaortic stenosis). On the other hand, when transposition of the great arteries with ventricular septal defect has accompanying subpulmonic stenosis, the outlet septum is deviated leftwards and actually has come through the ventricular septal defect. The outlet septum is attached to the anterolateral muscle bundle of the left ventricle thus producing obstruction to the subpulmonic outflow tract, and some degree of override of the aortic valve over the ventricular septum. In these cases there also may be an extension of a fibrous shelf from the underside of the outlet septum across the outflow tract and onto the surface of the mitral valve. This shelf may worsen the stenosis produced by the deviation of the outlet septum or itself produce stenosis. In patients with transposition of the great arteries and ventricular septal defect, as in patients with an intact interventricular septum, subpulmonic stenosis can also be produced by anomalous attachments of atrioventricular valve tension apparatus or fibrous tissue tags. In addition, in the presence of a ventricular septal defect, an aneurysm of the membranous septum may be present and cause subpulmonic stenosis. In reality this is usually a pouch of tricuspid valve tissue that prolapses during systole through the ventricular septal defect and into the left ventricular outflow tract.[35,37] In some cases a redundant portion of the mitral valve, rather than tricuspid valve tissue, may be responsible for this systolic bulge. In either case, it is important to recognize that these structures represent atrioventricular valve tissue since wide excision at the time of repair may result in postoperative atrioventricular valve regurgitation.

Other Complicating Lesions

Patent Ductus Arteriosus

This structure is usually present in all newborns with transposition and most often closes spontaneously in the first few days of life. In patients with transposition and an intact interventricular septum, closure of the ductus arteriosus results in profound hypoxemia and is usually the event that precipitates referral of the patient for evaluation. Although patency of the ductus arteriosus is important in the early management of the patient with transposition as can be readily demonstrated by the administration of prostaglandin E_1, persistent patency of the ductus arteriosus can be a difficult management problem.[38] A large persistent ductus arteriosus may lead to congestive heart failure and put the patient at risk for developing pulmonary vascular disease.

Coarctation of the Aorta

This lesion is present in about 5% of patients with transposition of the great arteries.[24] It is more commonly associated with ventricular septal defect but on occasion may be present when there is an intact interventricular septum. Interruption of the aortic arch is a rare, though well-recognized, association with transposition of the great arteries.[5]

Other Cardiac Anomalies

In addition to those anomalies mentioned above, other anomalies that are infrequently present in association with transposition of the great arteries include some aortic arch anomalies, various types of partial or total anomalous pulmonary venous drainage, systemic venous drainage anomalies, and cor triatriatum.[5]

ANATOMIC CLASSIFICATION

In the past, the main distinguishing features of the ventriculoarterial junction (the connection, the relationships and the infundibular morphology) have been used individually or collectively to describe transposition of the great arteries.[11,12,14] This has led to controversy as to whose definition of transposition is more correct.[13,15] In addition, if one considers great vessel relationships or infundibular morphology in the definition of transposition, then exceptions immediately must be put forth in order to explain the variations from the rules.[12] The discordant ventriculoarterial connection is the only distinguishing characteristic that is the hallmark of transposition of the great arteries and always produces the clinical picture that we recognize as transposition.

Relationships

The relationship of the great arteries is variable within the chamber combinations that produce the clinical picture of transposition

of the great arteries. In 60% of the patients, the aorta is anterior and to the right of the pulmonary artery. The classification of Van Praagh, which describes transposition on the basis of relative great artery position and thus their "D" or "L" relationship, would term this to be "D transposition."[11] There are problems with this classification. The aorta may be anterior to the pulmonary artery but may also be located to its left. The Van Praagh classification will need to use a different term ("L transposition") to describe this anatomy. In addition, if a rotational anomaly is present, a heart may actually have the pulmonary artery anterior and spiraling around the aorta, as is seen in a normal great artery relationship, despite the presence of ventriculoarterial discordance.[12] In situs inversus with mirror image arrangement, the Van Praagh classification scheme will classify atrioventricular concordance and ventriculoarterial discordance separately as "L-loop of the ventricles and L-transposition." It is clearly more difficult and confusing to use this method to describe the various types of anatomic variations of ventriculoarterial discordance that produce the clinical picture of transposition of the great arteries.

Infundibular Morphology

In the majority of hearts with transposition of the great arteries, there is a subaortic infundibulum and fibrous continuity between the mitral valve and the pulmonary valve. However, in hearts with a ventricular septal defect, there may be a muscle ridge that forms a wedge of tissue that separates the attachment of the mitral valve from the attachment of the pulmonary valve. In addition, a muscle ridge from the interventricular septum may also be present that almost forms an infundibulum where it merges with the parietal muscle bar. In a minority of hearts with transposition of the great arteries, there may actually be a large subpulmonary muscular infundibulum. Usually, this muscle structure is nothing more than the inner curvature of the heart (the inner lining of the transverse sinus between the posterior aspect of the pulmonary artery and the anterior aspect of the atrium). In general this structure is attenuated to permit fibrous continuity between the mitral valve and the pulmonary valve, but this is not always true. Thus, if one defines transposition of the great arteries on the basis of absence of a subpulmonary infundibulum, then all of these hearts without fibrous mitral-pulmonary valve continuity would not fit into this classification. However, the presence of a subpulmonary muscular structure in each of these situations does not alter the circulatory pathway nor does it even alter the surgical approach. Thus, these hearts with discordant ventriculoarterial connections and with a subpulmonary muscular structure and fibrous discontinuity between the mitral and pulmonary valves are still appropriately classified as having transposition.

As can be seen from the above brief discussion, "typical" great artery relationships and infundibular morphology are commonly present in the heart with transposition. Because differences can occur, however, it is not possible to make the diagnosis of transposition based on these features alone.

For the clinician, the fine points of anatomic detail that may separate the various types of transposition and different classifications are more of academic interest. In general, it is the presence or absence of associated cardiac anomalies that dictate the presentation, clinical course, and eventual surgical approach to the management of these patients. With this in mind the subsequent discussion in this chapter will focus on three main broad categories of patients with transposition of the great arteries.

1. Transposition with intact interventricular septum (complete transposition)—the heart with atrioventricular concordance and ventriculoarterial discordance regardless of atrial situs or heart position. These may or may not have left ventricular outflow tract obstruction.
2. Transposition with ventricular septal defect—hearts with complete transposition and an interventricular communication that do not have narrowing in the left ventricular outflow tract.
3. Complex transposition—these include hearts with complete transposition, ventricular septal defect, and varying degrees of left ventricular outflow tract obstruction. These are usually characterized by significant subpulmonic stenosis and equal right and left ventricular pressures. Included in this category are some patients with pulmonary atresia. Some cases have varying degrees of hypoplasia of the right ventricle.

This anatomic arrangement in transposition of the great arteries, concordant atrioventricular connection with discordant ventriculoarterial connection, is present in both situs solitus and situs inversus. This same clinical picture is produced by a discordant atrioventricular connection with concordant (normal) ventriculoarterial connection. In this lesion, termed "isolated ventricular inversion," the systemic venous blood passes from the right atrium into a morphologically left ventricle, which is connected to an aorta. Pulmonary venous blood is pumped into the lungs by a morphologic right ventricle connected to the left atrium and pulmonary artery. The internal cardiac anatomy is what would be expected for the respective ventricles and their connections. This lesion is discussed further in Chapter 73 on Ventricular Inversion.

EMBRYOLOGY

There are a number of different theories to explain the embryologic origin of transposition of the great arteries. Since substantial controversy still exists regarding the definition and classification of transposition, it is not surprising that a similar debate continues regarding the hypotheses of embryologic development. Fortunately, the intracardiac structures in hearts with transposition of the great arteries generally have developed normally. Thus, the controversy is centered around hypotheses that explain the abnormality of conotruncal development. Only a brief summary of the embryology of transposition will be presented here. A detailed description of normal morphogenesis can be found in Chapter 2 in this text while a number of excellent references provide a detailed overview of the embrylogic hypotheses (Anderson et al., 1974[39,40]; de la Cruz et al., 1974[41] and 1981[42]; Goor et al., 1972[43]; Shaher 1973[5]; and Van Mierop et al., 1963[44]).

A number of events take place during embryonic cardiac development that result in normal connection and relationship of the great arteries. These include shifting of the bulbus cordis or conus region to the midline, twisting of the conus region, and septation of the great arteries. In 1909 Keith[45] proposed the differential conal absorption hypothesis to explain the production of transposition of the great arteries. This has undergone a number of modifications so that the current theories include both abnormal canal growth and absorption leading to discordant ventriculoarterial connec-

tions.[42] In normal embryologic development, a bilateral conus develops beneath the aorta and the pulmonary artery. At that stage the developing aortic valve is to the right and the pulmonary valve to the left. According to this theory, there is further development of the subpulmonary conus and absorption of the subaortic conus. This differential of growth and absorption results in the pulmonary valve being elevated and pushed anteriorly, thus coming to lie over the right ventricular outflow tract; while the aortic valve descends posteriorly and rightward thus coming to rest over the left ventricular outflow tract. In transposition of the great arteries, the reverse occurs. The subaortic conus continues to develop and the subpulmonary conus is absorbed. The aorta then is moved superiorly and anteriorly and remains to the right. The absorption of the subpulmonary conus results in the pulmonary valve migrating inferiorly, posteriorly, and remaining to the left.

Another hypothesis was that transposition of the great arteries occurred as a result of abnormal formation of the aortopulmonary septum.[44] This septum normally develops in spiral fashion to separate the truncus arteriosus and it was theorized that abnormal fusion of the truncal ridges resulted in septation of the truncus arteriosus in a straight fashion thus producing an anterior aorta and posterior pulmonary artery.

Unfortunately neither of these theories is able to explain completely all of the various anatomic and positional abnormalities that occur in hearts with ventriculoarterial discordance. Although each provides a seemingly valid explanation for the more common forms of transposition, it is necessary to combine both of these hypotheses to explain the more unusual forms.[42] In addition, current research in experimental embryology continues to provide new and interesting information regarding cardiac morphogenesis. It has recently been demonstrated that a specific region of neural crest tissue contributes cells to the developing truncal septal region and outflow tract of the heart and that damage to this area results in conotruncal abnormalities.[46] However, since a specific embryologic model of transposition of the great arteries still does not exist, these embryologic hypotheses still remain to be validated in the future.

EPIDEMIOLOGY AND GENETICS

The incidence of transposition of the great arteries is approximately 5% of infants born with congenital heart disease. The incidence reported in any study is dependent upon the nature of the series and what group of patients with transposition were included or excluded from the numerator. In 1973, Campbell[4] summarized seven series describing the incidence of different cardiac malformations at birth. The overall incidence of transposition of the great arteries was 4.2% with a range in each series from 2.5 to 11%. Hoffman and Christianson[1] evaluated congenital heart disease in a cohort of 19,502 births. They reported a 3.7% incidence of transposition of the great arteries. When their data were combined with the data from six other series, transposition was found in 4.7% of over 3000 infants with congenital heart disease. The incidence reported in these other studies ranged from a low of 2.6% to a high of 7.8%. In the largest prospective survey, Mitchell, et al.[47] found the incidence of transposition to be 2.6% of live births with congenital heart disease in a cohort of over 56,000 total births. Thus, the actual incidence of transposition of the great arteries is difficult to determine exactly.

The etiology of transposition of the great arteries remains obscure. Despite the ever increasing range of reported hereditary syndromes, chromosomal abnormalities or other congenital malformations, transposition of the great arteries is rarely associated with these syndromes. In addition, extracardiac malformations are relatively infrequent (less than 7%) and are generally minor in patients with transposition.[48] In general, transposition of the great arteries appears to occur sporadically and is not familial. However, it has been found to occur in greater frequency in siblings of patients with transposition than would be expected to occur on the basis of its frequency in the general population.[49,50] This suggests a multifactorial inheritance resulting from genetic-environmental interaction with the environmental factor playing a major role.[50] Of note is the fact that transposition was not reported to have occurred in the offspring of a large group of mothers with congenital cardiac anomalies.[51] However, very few of these mothers had transposition of the great arteries themselves and it remains to be seen what the outcome of pregnancies in mothers with transposition will be as they reach child-bearing age. In view of the absence of a familial incidence or genetic inheritance patterns for transposition of the great arteries, the fact that the male-to-female ratio is approximately 2:1 in most series is surprising and needs to be explained. Despite this sex difference, there does not appear to be a racial predilection[52] or any other epidemiologic factor. No specific etiologic agent has been identified. However, transposition is seen more frequently than expected in infants of diabetic mothers.[3,53] Nora and Nora[50] suggested that in addition to diabetes, other potential environmental teratogenic agents may have a role in producing transposition. These include amphetamines, trimethadione, and sex hormones.

PHYSIOLOGY AND HEMODYNAMICS

In the normal heart, the circulation is connected in series. The systemic venous return passes into the pulmonary artery while the pulmonary venous return passes into the systemic arterial circulation. In the heart with transposition of the great arteries, the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. Since the atrioventricular connections are normal, the result of this abnormal arterial connection is that the circulation is no longer in series. Instead, there are now two separate parallel circulations (Fig. 71–3). The systemic venous return passes through the right heart and is ejected into the aorta, while the pulmonary venous return passes through the left heart and is again ejected into the pulmonary artery. This physiologic arrangement is incompatible with life unless some means exists for mixing of blood between the two circulations (Fig. 71–4). In the neonate with transposition of the great arteries and an intact interventricular septum, a foramen ovale or atrial septal defect is usually present and facilitates bidirectional exchange of blood at the atrial level. In addition, the presence of a patent ductus arteriosus enhances this exchange, allowing for blood to pass from aorta to pulmonary artery at the level of the ductus and pass in the opposite direction from the left side of the heart to the right side of the heart at the atrial level. If there is no intra-atrial communication, this exchange must occur at ventricular level, during diastole, in a similar direction. In the absence of an intracardiac communication, the patient will not survive since bidirectional shunting usually does not occur at ductal level. Unfortunately the ductus arteriosus is

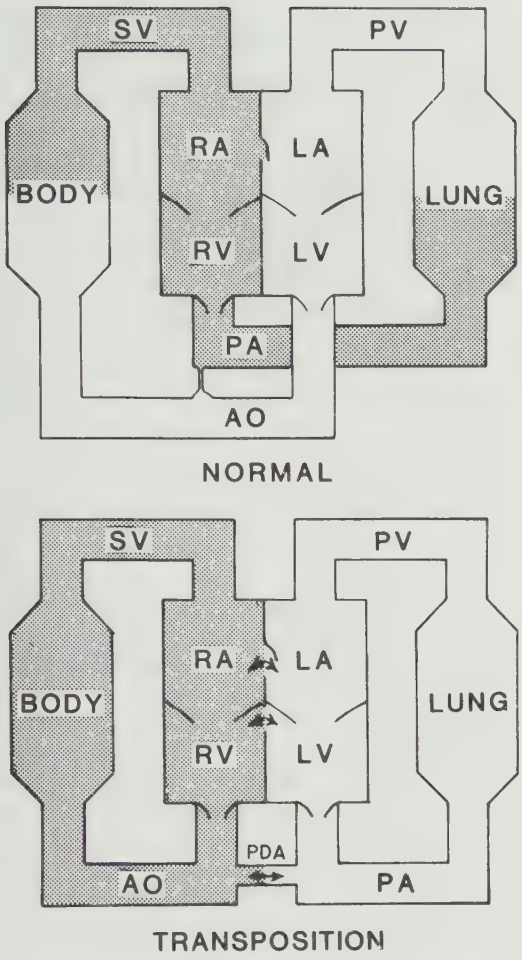

Fig. 71–3. Diagram of the circulatory pathways in transposition of the great arteries. AO = aorta, PV = pulmonary veins, LA = left atrium, RA = right atrium, LV = left ventricle, RV = right ventricle, PA = pulmonary artery, SV = systemic veins, PDA = patent ductus arteriosus.

usually a transient neonatal structure and tends to close physiologically within a few days after birth. The closure of the ductus is the event that precipitates a dramatic change in the clinical appearance of the patient from an apparently healthy newborn to one with intense cyanosis. The importance of the ductus arteriosus in providing a route for this interchange between the two circulations is graphically demonstrated on a continuing basis to clinicians who care for these patients. Prior to balloon atrial septostomy and sometimes even afterwards, the administration of prostaglandin E_1 to maintain patency of the ductus arteriosus usually results in a dramatic improvement in the patient's arterial oxygen saturation. However, if an adequate intra-atrial communication is not present, pulmonary venous congestion may result. Conversely, if this drug is withdrawn prior to the creation of an adequate interatrial communication, the patient will usually develop intense cyanosis within a short period of time.

The patient with transposition of the great arteries and a significant sized ventricular septal defect presents an entirely different clinical picture. These patients often have adequate exchange of blood with a combination of mixing at atrial and ventricular levels.

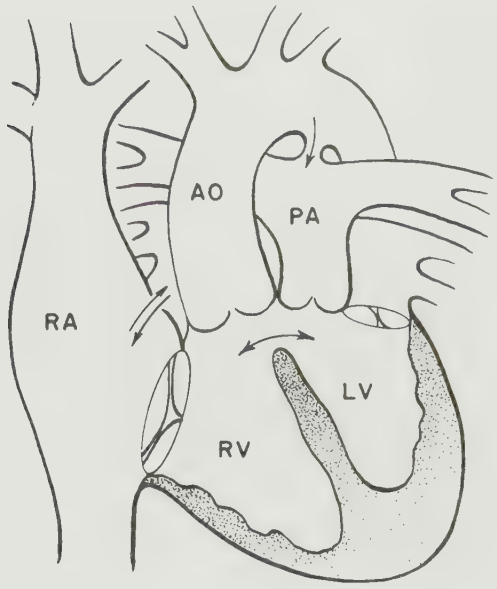

Fig. 71–4. Diagram of a heart with transposition of the great arteries indicating the possible sites of mixing of blood between the systemic and pulmonary circulations (arrows). See Fig. 71–3 for legend to abbreviations.

Shunting is generally bidirectional although it is predominantly from right ventricle to left at ventricular level and from left to right at atrial level. As a result of the adequacy of blood exchange at atrial and ventricular levels, these patients are only mildly cyanotic in the early neonatal period and therefore the presence of a significant cardiovascular anomaly may not be suspected until a few weeks later.

The behavior of the muscular arterioles of the pulmonary vascular bed in infants with transposition of the great arteries is similar to that in patients with other anomalies.[54] Despite the large amount of pulmonary blood flow in patients with transposition of the great arteries and an intact interventricular septum, pulmonary vascular resistance begins to fall within a few days after birth. This facilitates the flow of blood from the aorta into the pulmonary artery as long as the ductus arteriosus remains open. In the presence of a ventricular septal defect, the initial drop in pulmonary vascular resistance at a few days of age promotes increased shunting at the ventricular level. This increase in pulmonary blood flow results in a prompt increase in the tone of the muscular pulmonary arterioles. As a result of this renewal of arteriolar tone, the degree of shunting at ventricular level is again reduced and thus the signs and symptoms of congestive heart failure are temporarily averted. Thus, in transposition with a large ventricular septal defect, the pulmonary and systemic vascular resistances remain relatively balanced for a period of about 3 to 6 weeks. As occurs in other congenital cardiac anomalies that are associated with shunting at ventricular level and significantly increased pulmonary blood flow, the pulmonary arterioles gradually lose their muscular tone by about 3 to 6 weeks of age. This results in the appearance of the clinical symptoms of congestive heart failure toward the end of the first month of life.

The physiology in patients with complex transposition (transposition of the great arteries, ventricular septal defect, and pul-

monary stenosis) differs from either of the other two clinical forms. In patients with transposition and an intact interventricular septum, symptoms appear in early life and are due to poor mixing of the separate parallel circulations. In transposition and ventricular septal defect, cyanosis is not the major problem. These patients present with congestive heart failure toward the end of the first month of life as a result of extremely large pulmonary blood flow. In patients with complex transposition there is a large ventricular septal defect and the balance between pulmonary and systemic blood flow is dependent upon the degree of pulmonary stenosis. Thus, these patients have a physiologic situation similar to patients with tetralogy of Fallot. In the presence of severe pulmonary stenosis or pulmonary atresia, these patients present with cyanosis and reduced pulmonary blood flow in the early days of life. On the other hand, if the degree of pulmonary stenosis is less severe, then clinical presentation is due to the presence of cyanosis and/or the detection of a heart murmur and may occur even later in infancy.

The neonate with transposition of the great arteries and an intact interventricular septum usually has a significant degree of hypoxemia with systemic arterial Po_2 in the low 30s and often even less than that. This low level of arterial oxygenation is surprisingly well tolerated by many neonates with transposition. It is likely that the polycythemia normally present in the neonate results in the ability for adequate oxygen delivery to the tissues. Thus, these infants often have a normal pH or a relatively mild degree of compensated metabolic acidosis in the first few days of life.

CLINICAL FEATURES

Cyanosis of the mucous membranes and nailbeds is an almost universal clinical feature of the infant with transposition of the great arteries and an intact interventricular septum. However, the intensity of this cyanosis can be modified by the presence of associated abnormalities. Thus, the presence of a patent ductus arteriosus and an adequate interatrial communication in the neonate may sufficiently facilitate mixing so as to make cyanosis not apparent at rest. A large ventricular septal defect may have a similar effect and may even provide adequate enough mixing so that the infant may not appear cyanotic even with exercise such as crying or feeding. Similarly, in patients with complex transposition (ventricular septal defect and pulmonic stenosis) the degree of pulmonic stenosis may be sufficient to provide just the right balance between pulmonary and systemic blood flow. Thus, the patient with complex transposition may be cyanotic or mildly cyanotic at rest but usually will have significant cyanosis at the time of exercise.

The right ventricle is the systemic ventricle in the patient with transposition of the great arteries. Thus, a prominent parasternal impulse indicating hyperdynamic motion and hypertrophy of the underlying right ventricle is usually appreciated on palpation of the precordial area. As a result of the usual anatomic relationship with the aorta being anterior to the pulmonary artery, the loud high velocity closure of the aortic valve is usually magnified. Thus, the second heart sound is often palpable in the patient with transposition.

On auscultation the second heart sound is usually single. This results from the loud closure sound of the anterior aorta and the fact that the soft closure sound of the pulmonic valve is difficult to appreciate due to its posterior location within the chest. However, in some patients with transposition it may be possible to hear splitting of the second heart sound. In the neonate and infant with transposition of the great arteries and an intact interventricular septum there is usually no murmur present on auscultation. This may also be true in the older child with this anatomy. However, since there is often some degree of dynamic left ventricular outflow tract obstruction in most patients with transposition past the period of infancy, it is common to find a soft grade I or II/VI systolic ejection murmur present at the mid to upper left sternal border. It is important to note that although this systolic ejection murmur is commonly present, the absence of a murmur in a patient with transposition and intact interventricular septum does not preclude the presence of substantial left ventricular outflow tract obstruction. We have seen a few patients with left ventricular pressure at systemic level and a left ventricular outflow tract gradient of 70 or 80 mm Hg who had no murmur on auscultation.

When there is a ventricular septal defect, a plateau pansystolic murmur is usually present at the lower left sternal border. As in the normal heart, there is an inverse relationship between the size of the ventricular septal defect and the intensity of the murmur with louder murmurs usually produced by smaller defects. It is interesting to note that despite the presence of increased pulmonary blood flow in patients with transposition and an intact interventricular septum or a ventricular septal defect it is unusual to hear the diastolic murmur that one associates with increased flow across the mitral valve in the heart with normally related great arteries.

Patients with complex transposition have a physiologic situation similar to the patient with tetralogy of Fallot. As a general rule in these patients, there is an ejection murmur along the upper left sternal border. The intensity of this murmur, as in the patient with tetralogy, has an inverse relationship to the degree of subpulmonic outflow obstruction. Patients with a moderate degree of obstruction have a prominent murmur while those with more severe degrees of obstruction usually have a soft murmur.

NONINVASIVE STUDIES

Electrocardiogram

Right axis deviation and right ventricular hypertrophy are present on the electrocardiogram in the patient with transposition of the great arteries. Since this is the normal pattern seen in the newborn it is not possible to suspect the presence of transposition on the basis of this finding on electrocardiogram (nor to differentiate it from any other type of congenital heart disease that may show a similar pattern in the neonate). In the patient with transposition, this pattern persists as long as the right ventricle remains the systemic ventricle. Thus, the patient who has undergone an atrial baffle repair, such as a Mustard or Senning operation, will continue to have electrocardiographic signs of right ventricular hypertrophy throughout life. In children with an associated ventricular septal defect and/or pulmonic stenosis, the presence of a hypertrophied left ventricle may alter the usual dominance of the right ventricle and result in the pattern of biventricular hypertrophy. Hypoplasia of the right ventricle should be suspected when right ventricular hypertrophy is absent in a patient with transposition and a ventricular septal defect. It is also important to note that on occasion, the usual right ventricular hypertrophy may not be found

in the patient with transposition of the great arteries even with an intact interventricular septum. Although this is uncommon in the patient with transposition, the absence of right ventricular hypertrophy on electrocardiogram cannot be construed as an indication that transposition is not present.

Right atrial enlargement, as evidenced by narrow peaked P waves of greater than 2.5 mm in height, is occasionally found on the electrocardiogram of a patient with transposition. Left atrial enlargement is generally not seen despite the large volume of blood that is handled by the left atrium in patients with this abnormality. Arrhythmias are uncommon in the unoperated patient with transposition. However, following atrial baffle procedures, patients are often found to have atrioventricular dissociation with junctional rhythm. Various types of atrial bradyarrythmias and tachyarrhythmias, indicating the presence of sick sinus syndrome, are commonly found a number of years postoperatively in patients who have undergone atrial baffle repair. These problems will be discussed in more detail in the section dealing with surgical followup later in this chapter.

Radiography

In general, the neonate with transposition of the great arteries has a normal chest roentgenogram. In about one-third of infants with transposition and an intact interventricular septum, what has been described as a "classic" transposition chest roentgenogram is seen (Fig. 71–5). In these patients the mediastinal shadow is narrow, probably due to the anteroposterior relationship of the great arteries that is often found in this anomaly. The heart is somewhat ovoid and the resulting image is what has been described as an "egg on a string." Although this has been the classically described radiographic pattern, it can be seen in normal patients with a small or absent thymus, or in patients with other congenital cardiac anomalies. In addition, the absence of this radiographic pattern by no means precludes the presence of transposition of the great arteries.

After the first few days of life, the patient with transposition and an intact interventricular septum has increased pulmonary blood flow and will usually have increased pulmonary vascular markings radiographically. Cardiomegaly is generally not seen. However, it may be found if congestive heart failure is present and balloon atrial septostomy as yet has not been performed. Patients with other forms of transposition will exhibit the radiographic pattern that would be expected on the basis of their associated anomalies. Thus, patients with an associated ventricular septal defect will usually have cardiomegaly and increased pulmonary vascular markings. If severe congestive heart failure is present, a pulmonary venous pattern may also be found radiographically. In the patient with complex transposition the heart size is usually normal and the pulmonary vascular markings are normal; if severe pulmonary stenosis or pulmonary atresia is present, the pulmonary vascular markings are decreased.

There are some important features of the pulmonary vascular markings in the patient with transposition that need to be stressed. In the patient with transposition and an intact interventricular septum, there may be a discrepancy between the blood flow to the right and left pulmonary arteries.[55] In many cases, approximately two-thirds of the output of the left ventricle may be directed preferentially to the right lung. This may result in a greater increase in the pulmonary vascular markings of the right lung as compared to the left.

Echocardiography

In the past, cyanotic infants required urgent cardiac catheterization to establish an anatomic diagnosis and plan the approach to management. With the advent of M-mode echocardiography, a variety of findings were described in association with transposition. Although the simultaneous visualization of both great arteries reflects their anteroposterior relationship in transposition,[56] this relationship can also be found in children with other forms of congenital heart disease, as well as in normal infants.[57] The determination of systolic time intervals in the patient with transposition reveals that the posterior great vessel (usually the pulmonary artery) opens before and closes after the anterior aorta.[58]

Fig. 71–5. Chest roentgenogram in transposition of the great arteries (see text).

However, this does not always hold true especially when there is an increase in the left ventricular afterload. Imaging of both great vessels from the suprasternal notch position together with a peripheral injection of echocardiographic contrast material has also been employed. From this angle, the aorta is almost always anterior to the pulmonary artery.[59] Although early opacification of the anterior vessel occurs in transposition, it is also found with other anomalies and in the presence of significant bidirectional shunting. Thus, although the diagnosis of transposition of the great arteries may be suspected, it cannot be made reliably on the basis of M-mode echocardiography alone, since false positive or equivocal findings are often present.

Two-dimensional echocardiography has had a dramatic impact on the noninvasive diagnosis of transposition of the great arteries. With this technique it is now possible reliably to demonstrate the atrioventricular and ventriculoarterial connections. Cross-sectional images obtained from different views will demonstrate that the aorta arises from a morphologic right ventricle that receives the systemic venous return and the pulmonary artery arises from a morphologic left ventricle.[60] Thus, it is possible to demonstrate the presence of the physiologic and anatomic abnormalities that give rise to the clinical picture of transposition of the great arteries regardless of the position of the heart within the chest or the relationship of the great arteries. All of the echocardiographic modalities, two-dimensional, M-mode, and Doppler echocardiography, are important in demonstrating the associated lesions and physiologic derangements that can occur in the patient with transposition.

While performing the echocardiographic scan, it is advisable to follow a systematic sequential approach in order to delineate the presence or absence of certain abnormalities at each specific step. This reduces the possibility of overlooking any abnormalities. It is important to determine the situs in each patient, and this should be done from the subcostal position at the beginning of each study. In situs solitus, a short axis view of the abdominal vessels at the level of the diaphragm shows the inferior vena cava to the right of the spine and the aorta to the left. Clockwise rotation of the transducer to obtain a longitudinal view allows tracing of the inferior vena cava to the right-sided atrium. In situs inversus, the aorta lies to the right of the spine. The inferior vena cava is on the left side and drains to the left-sided atrium.[61]

In the patient with situs solitus, the parasternal long axis view will demonstrate fibrous continuity between the mitral valve and the posterior arterial valve (Fig. 71–6). Following the course of this great artery by gentle clockwise rotation and superior angulation of the transducer allows differentiation between an aorta and a pulmonary artery. An aorta will continue in a cephalad course before it turns posteriorly to become the aortic arch and give off the brachiocephalic branches, whereas a pulmonary artery will dip posteriorly shortly after its origin (Fig. 71–6). A usual, but not consistent, finding is the visualization of both great arteries in a parallel alignment. This is not pathognomonic of transposition of the great arteries since it is often seen in different varieties of double outlet right ventricle. In contrast, in the normal heart with concordant ventriculoarterial connections, the great arteries cross over each other as a result of their spiral relationship.

Defects in the interventricular septum, particularly when there is malalignment of the outlet portion, can also be identified from the parasternal long axis view (Fig. 71–7A). Posterior deviation

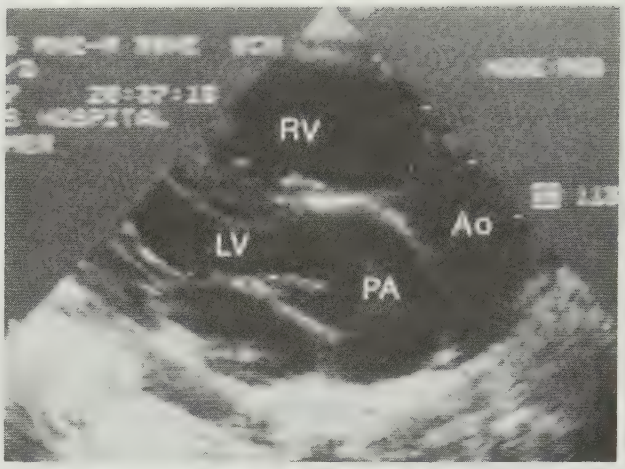

Fig. 71–6. Echocardiography—parasternal long axis view showing the pulmonary artery arising from the left ventricle and the aorta arising from the right ventricle. See Fig. 71–3 for legend to abbreviations.

of the outlet septum in transposition may produce significant left ventricular outflow obstruction (Fig. 71–7B).[62] In the absence of pulmonary hypertension and left ventricular outflow tract obstruction, the left ventricular pressure drops below systemic level beyond the neonatal period. As a consequence, the interventricular septum is usually seen to bulge posteriorly into the left ventricular outflow tract (Fig. 71–8). This is considered to be a result of the reversal of the normal pressure relationship between the right and left ventricles. Systolic anterior motion of the mitral valve may also be seen especially following an atrial baffle operation.

Clockwise rotation of the transducer will lead from a parasternal long-axis to a short-axis view. Cross-sectional imaging of both great arteries in short axis may reveal their abnormal relationship. Normally the pulmonary artery is anterior and to the left of the aorta. In transposition the aorta is generally anterior and to the right of the pulmonary artery (Fig. 71–9). However, it can be found directly in front, anterior, and to the left, or in the side-by-side relationship with the pulmonary artery. By gentle rotation and angulation of the transducer, the course of each great artery can be followed and their bifurcation patterns can be identified.[63] The aorta can be traced from the right ventricle and out of the cross-sectional field. It follows a long course before giving its first branch. The pulmonary artery typically bifurcates before the aorta and its origin from the left ventricle can be traced. This demonstration of ventriculoarterial discordance is essential for the echocardiographic diagnosis of transposition of the great arteries. Defects in the membranous portion of the interventricular septum, as well as patency of the ductus arteriosus, can also be demonstrated in this view. Caudal angulation will produce a short-axis view of both ventricles. Before surgical correction as well as after atrial baffle repair, the right ventricle appears dilated and hypertrophied. The interventricular septum is seen bulging posteriorly. The site of arterial anastomosis after the arterial switch operation is usually seen from the short-axis position.

An apical four-chamber view is obtained by placing the transducer at the apex and aiming medially. Analysis of the crux of the heart will show the normal "offset" between the atrioventricular valves. The tricuspid valve is more apically displaced than the mitral valve. This, together with visualization of dense apical

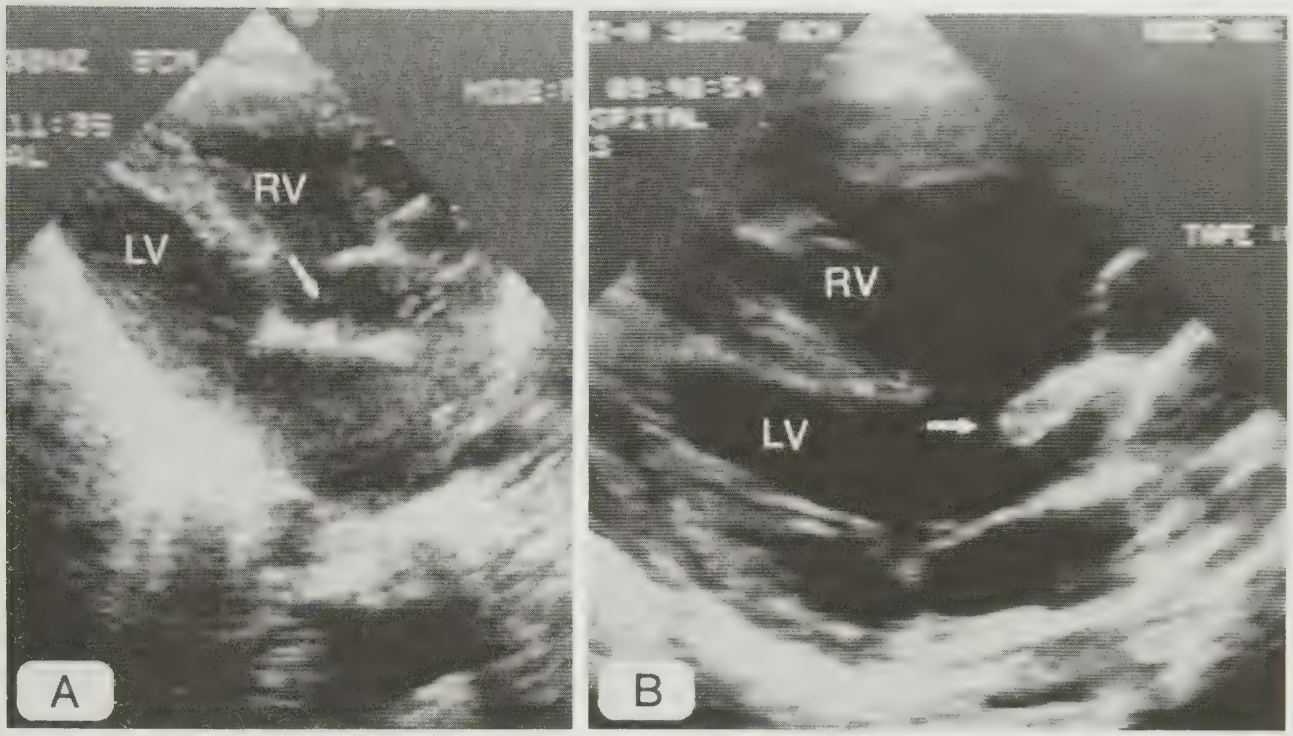

Fig. 71–7. Echocardiography—parasternal long axis view: (A) Malalignment ventricular septal defect. (B) Malalignment defect with posterior deviation of the septum causing left ventricular outflow obstruction (arrow). See Fig. 71–3 for legend to abbreviations.

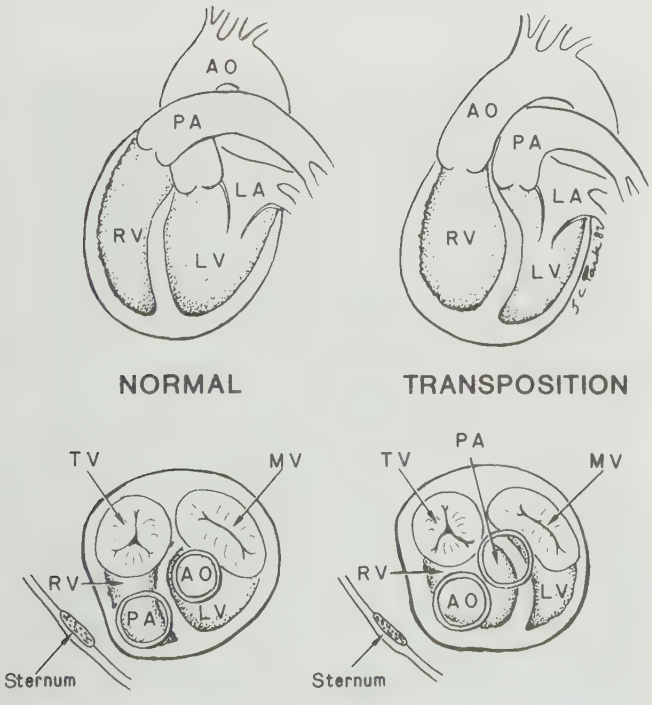

Fig. 71–8. Diagram demonstrating the posterior bulge of the interventricular septum in transposition of the great arteries. MV = mitral valve, TV = tricuspid valve.

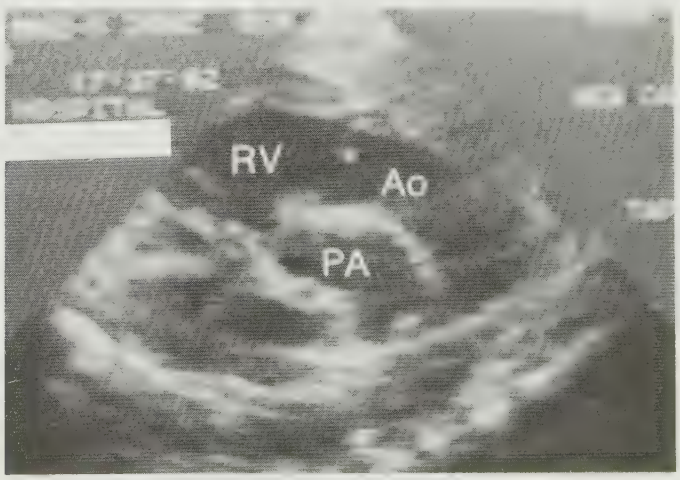

Fig. 71–9. Echocardiography—short-axis view demonstrating the anterior aorta arising from the right ventricle. See Fig. 71–3 for legend to abbreviations.

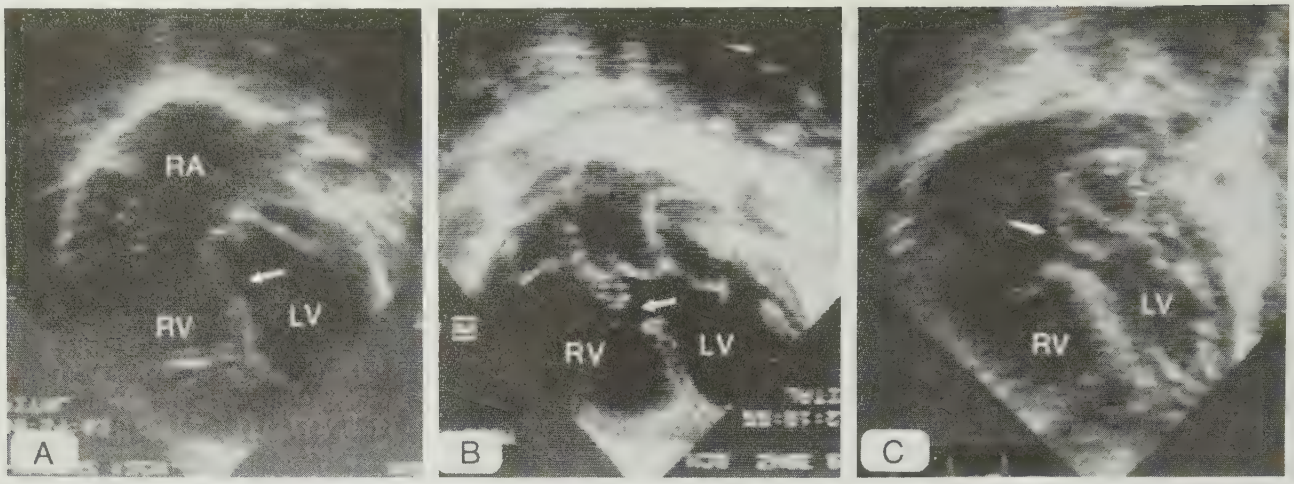

Fig. 71–10. Echocardiography—ventricular septal defects (arrows) in transposition of the great arteries. (A) Muscular inlet defect. (B) Trabecular muscular defect. (C) Inlet defect with straddling of the tricuspid valve. See Fig. 71–3 for legend to abbreviations.

trabeculations, allows the echocardiographic identification of the morphologic right ventricle. Defects in the inlet, trabecular and membranous portions of the interventricular septum can be profiled from this view (Fig. 71–10), as well as tricuspid valve and mitral valve abnormalities.[64] Cranial angulation of the transducer often shows the bifurcating pulmonary artery connecting to the left ventricle (Fig. 71–11). The interatrial septum is also seen but it is better visualized from the subcostal position. Pulmonary venous connections to the left atrium can be demonstrated. After the Mustard and the Senning operations, the anatomy of the interatrial baffle can be studied and obstruction to pulmonary and systemic venous drainage can be diagnosed (Figs. 71–12 and 71–13).[65,66]

The subcostal view is very helpful for demonstrating atrial structures and the pulmonary and systemic venous connections. Measurements of the interatrial communication before and after balloon or blade atrial septostomy can be performed serially from this angle (Fig. 71–14). A subcostal four-chamber view will provide additional information on the anatomy of the atrioventricular valves and the interventricular septum. From this four-chamber position, anterior angulation together with clockwise rotation of the transducer will profile the left ventricular outflow tract. The connection between the left ventricle and the pulmonary artery can be clearly demonstrated. Counterclockwise rotation from the above position will show the aorta arising from the right ventricle. Obstruction to the right ventricular outflow tract, right ventricular hypertrophy, and dilation are best assessed from this position.[67]

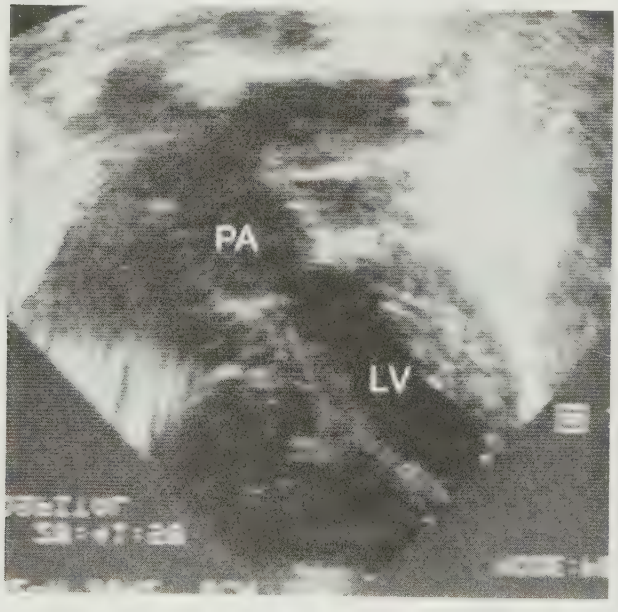

Fig. 71–11. Echocardiography—a four-chamber view demonstrating the pulmonary artery arising from the left ventricle. See Fig. 71–3 for legend to abbreviations.

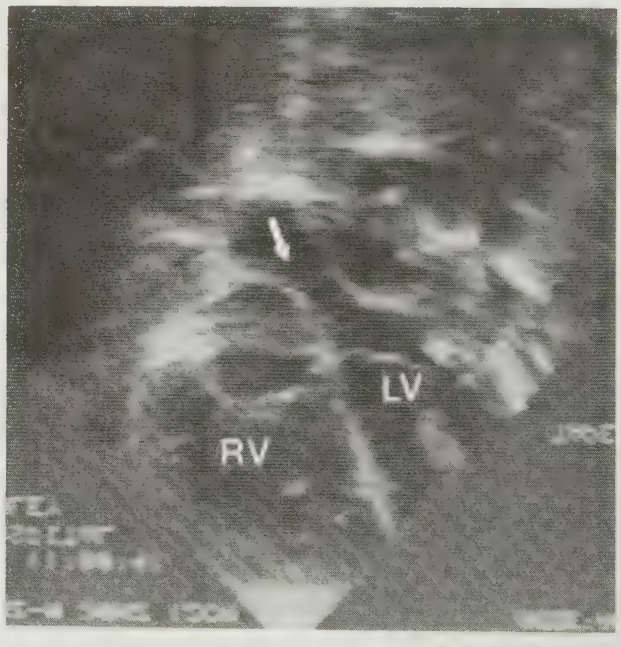

Fig. 71–12. Echocardiography—demonstration of systemic venous return (arrow) following atrial baffle operation. See Fig. 71–3 for legend to abbreviations.

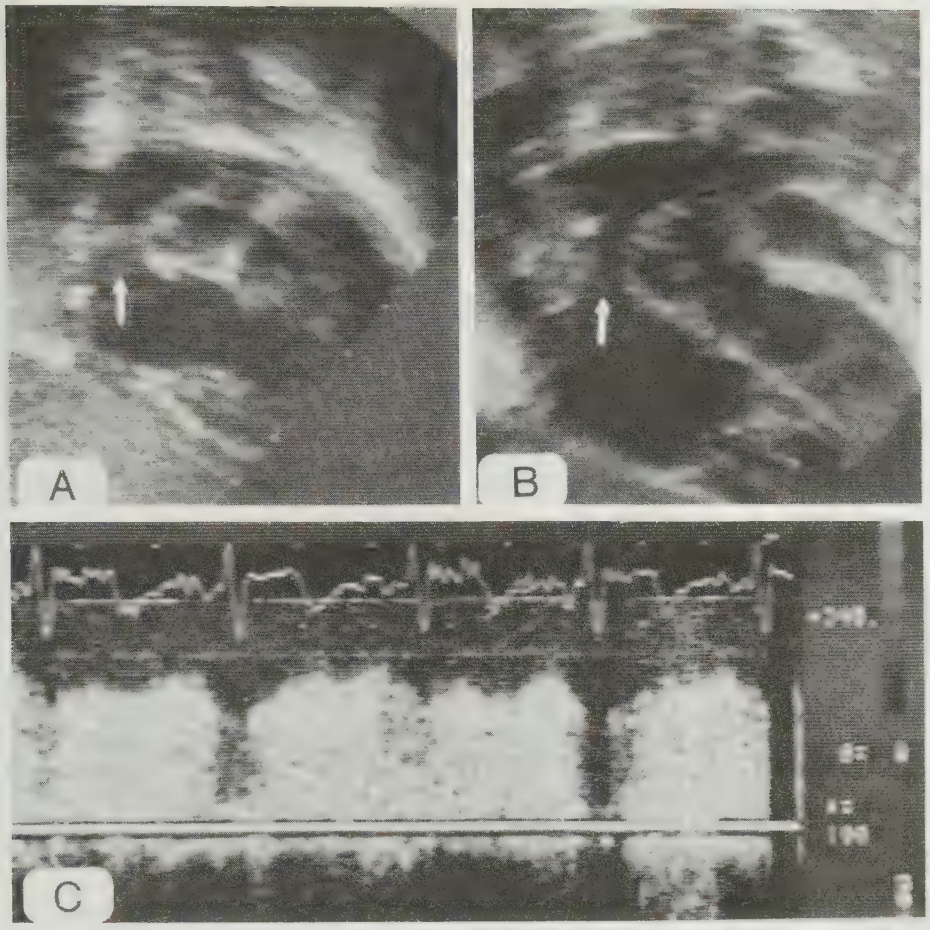

Fig. 71–13. Echocardiography—subcostal views demonstrating pulmonary venous return following atrial baffle operation. (A) Normal open drainage (arrow). (B) Obstructed drainage (arrow). (C) Continuous turbulent Doppler flow across the area of obstruction (maximum velocity = 2.3 m/sec).

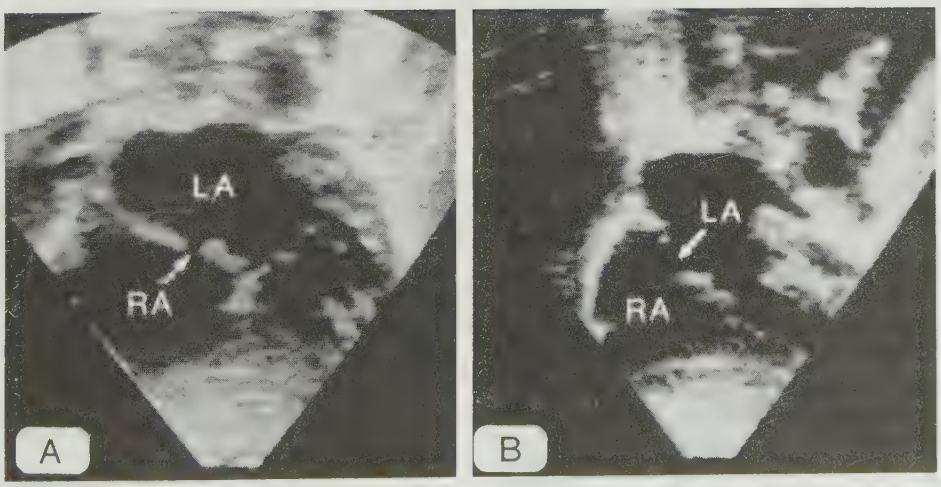

Fig. 71–14. Cross-sectional echocardiography in the subcostal view demonstrating the interatrial septum before (left) and after (right) balloon septostomy. See Fig. 71–3 for legend to abbreviations.

Stenosis of the arterial anastomosis after arterial switch repair can also be visualized from the subcostal window.

The anatomy of the aortic arch is best demonstrated from the suprasternal notch. Though uncommon, an associated coarctation of the aorta must be excluded. The ductus arteriosus is well seen using suprasternal views. Further information on the right and left pulmonary artery branches and the pulmonary venous connections can also be obtained.

It is possible to estimate systemic ventricular function in children with transposition of the great arteries using echocardiographic techniques. Serial assessment of right ventricular performance, especially after the Mustard or Senning operation is particularly useful in the longterm management of these patients. After the arterial switch operation, the left ventricle supports the systemic circulation. Good left ventricular function is important in this group and therefore echocardiographic measurements of left ventricular performance should be routinely obtained.

Pulse wave, continuous wave, and color Doppler echocardiography have added a new dimension to the noninvasive assessment of the patient with transposition of the great arteries. Function of the atrioventricular valves is best evaluated from the apical four-chamber position. These valves are usually normal in transposition. However, tricuspid regurgitation, particularly after atrial baffle repair, is common in the longterm. Doppler evaluation allows serial assessment of tricuspid regurgitation by "mapping" of the retrograde flow within the systemic venous atrium together with the duration and intensity of the regurgitant jet. Careful Doppler interrogation permits differentiation between tricuspid regurgitation and a small ventricular septal defect. The presence of small, multiple, or residual ventricular septal defects can also be evaluated by Doppler techniques (Fig. 71–15).

The right and left ventricular outflow tracts can also be studied with Doppler echocardiography. These areas need to be evaluated from the parasternal position, the suprasternal notch and the subcostal position. Left ventricular outflow tract obstruction is present in children with complex transposition but can also occur in patients with simple transposition both before and after atrial baffle repair (Fig. 71–16). In many cases, this is mild and due to dynamic bulging of the interventricular septum into the left ventricular outflow tract (see Fig. 71–8). In some cases, however, this may be progressive and additional hemodynamic changes may occur on the left ventricular surface of this septal bulge.[68] Doppler echocardiographic determination of the maximum flow velocity in the pulmonary artery provides an easy noninvasive method of assessing the degree of left ventricular outflow obstruction. After arterial switch repair of transposition of the great arteries, stenosis at the site of the arterial anastomosis can occur. The degree of obstruction can be easily quantitated using Doppler echocardiography (Fig. 71–17). Similarly, incompetence of the arterial valves can also be determined.

Flow across the interatrial septum and adequacy of balloon atrial septostomy can also be determined using Doppler echocardiography. Doppler techniques also contribute to the assessment of obstruction within the pulmonary and systemic venous atria after the Mustard and Senning operations. High velocity flows obtained by placing the pulse wave Doppler sample volume at the site of suspected obstruction confirms the diagnosis (see Fig. 71–13).

Apart from providing accurate anatomic and functional information, two-dimensional echocardiography has also altered the management of the newborn with transposition of the great arteries. Some centers will perform balloon atrial septostomy under echocardiographic control in the intensive care unit[69] or may use echocardiographic assistance in the catheterization laboratory, thus minimizing the risk of cardiac catheterization in neonates[70,71] (Fig. 71–18). Arterial switch operations are being performed more frequently in the neonatal period. A thorough echocardiogram may provide the cardiothoracic surgeon with the necessary anatomic information and may obviate the need for cardiac catheterization.

Two-dimensional and Doppler echocardiography represent very powerful tools for the noninvasive assessment of children with transposition of the great arteries. The combination of these techniques significantly reduces the need for cardiac catheterization especially in the newborn as well as in the longterm serial postoperative assessment of children with transposition.

CARDIAC CATHETERIZATION

Preoperative Indications

In the years prior to the 1980s, cardiac catheterization was the only means to make an accurate diagnosis of transposition of the

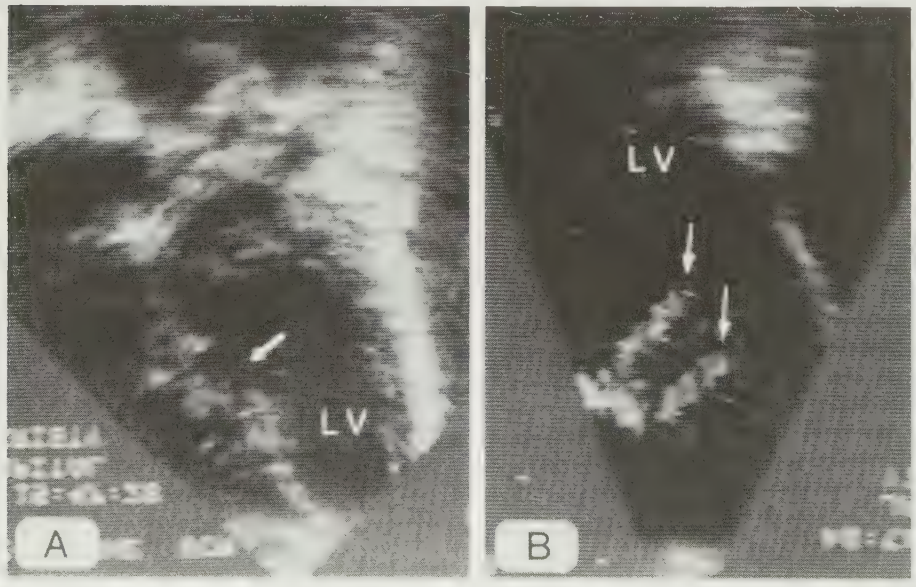

Fig. 71–15. Echocardiography. (A) Multiple muscular VSDs demonstrated by cross-sectional technique (arrow indicates area of defects). (B) The same defects visualized with color flow Doppler (arrows). See Fig. 71–3 for legend to abbreviations.

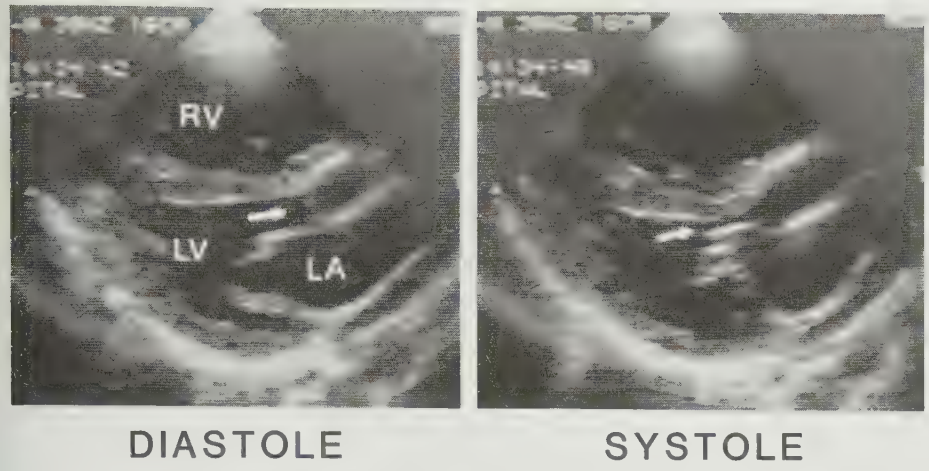

Fig. 71–16. Echocardiography demonstrating left ventricular outflow tract obstruction caused by systolic anterior motion of the mitral valve. Left: outflow tract is widely patent during diastole (arrow). Right: severe obstruction during systole (arrow). See Fig. 71–3 for legend to abbreviations.

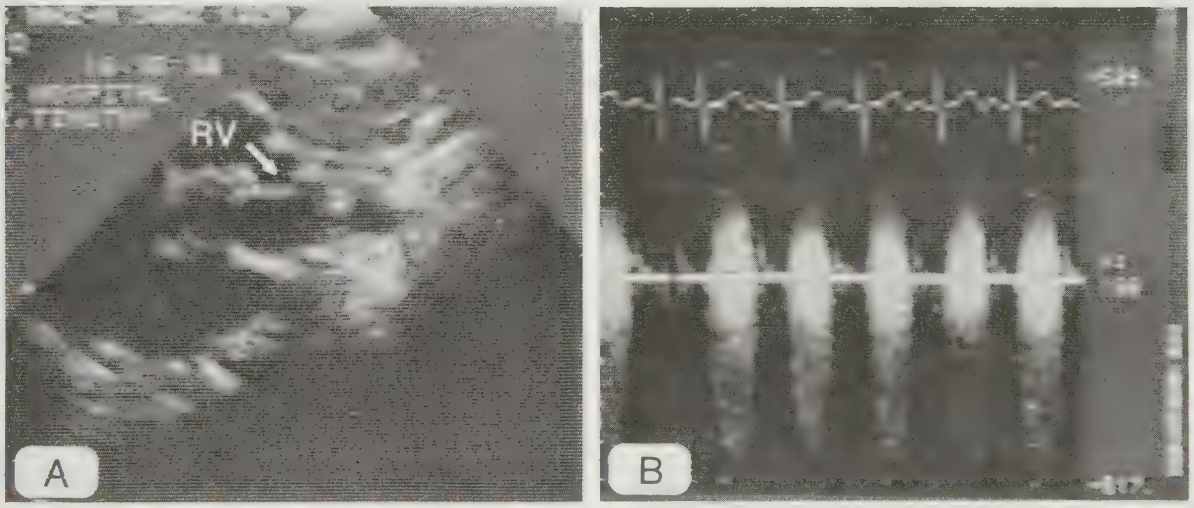

Fig. 71–17. Echocardiography—pulmonary artery stenosis following arterial switch repair. Left: short-axis view demonstrating supravalvar obstruction. Right: high velocity Doppler flow across the area of obstruction. See Fig. 71–3 for legend to abbreviations.

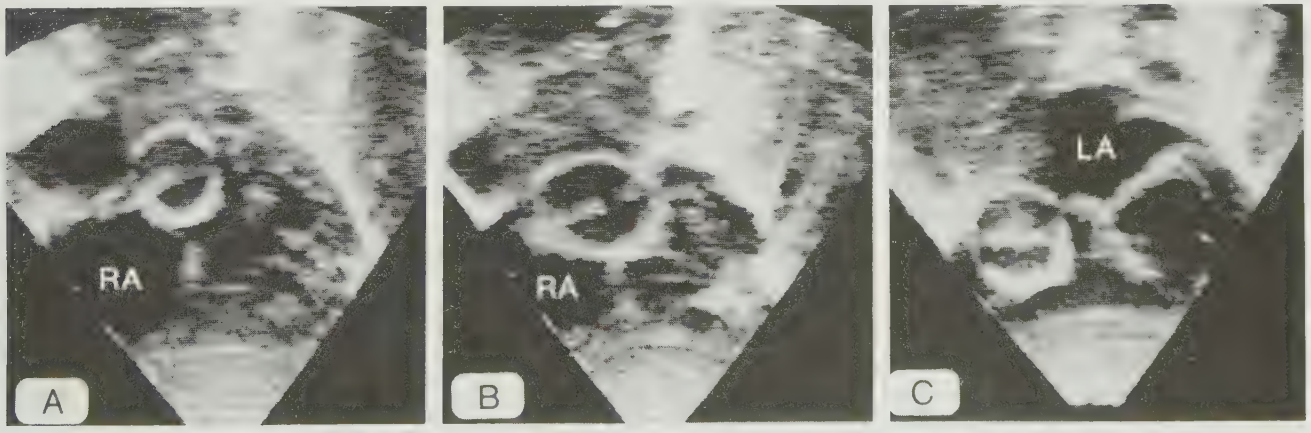

Fig. 71–18. Cross-sectional echocardiography from the subcostal approach demonstrating the balloon portion of a septostomy catheter during withdrawal from the left atrium to the right atrium. (A) Catheter in the left atrium. (B) Passage across the atrial septum. (C) Catheter in the right atrium. See Fig. 71–3 for legend to abbreviations.

great arteries. This was often performed as an emergency procedure on an extremely ill hypoxic newborn infant. In many cases only the minimum amount of necessary information was obtained and a balloon septostomy performed. In the 1980s the widespread availability of two-dimensional echocardiography made possible the accurate noninvasive diagnosis of transposition. In addition, the use of prostaglandin E_1 to maintain patency of the ductus arteriosus has provided the physician with the tool to decrease systemic hypoxemia and acidemia and thereby stabilize the sick neonate prior to any procedure. Cardiac catheterization can thus be performed much more safely. The patient is in much better condition and the major diagnosis has been established prior to the onset of the procedure. Thus, although the catheterization will confirm the diagnosis and evaluate for the presence and significance of associated anomalies, the major indication is to perform balloon atrial septostomy. Some centers have demonstrated that balloon atrial septostomy can safely be performed in the intensive care unit solely with echocardiographic guidance.[69,71] This may be valuable in a situation where the cardiac catheterization laboratory is not available and the procedure needs to be performed on an emergency basis. However, most centers still perform balloon atrial septostomy under fluoroscopy in the cardiac catheterization laboratory where all of the tools for diagnosis and management of unexpected emergency situations are readily available. Echocardiographic guidance may be useful, though is not essential in this situation.

Lastly, in considering the indications for cardiac catheterization and balloon artial septostomy in the newborn, one needs to take into account the expected method and timing of surgical therapy. If the patient is clinically stable, has responded to prostaglandin administration, and surgical repair is contemplated within a short period of time, then cardiac catheterization and balloon atrial septostomy are unnecessary. However, if there is concern about possible associated anomalies or if surgical repair is not contemplated for some time, then it is important to perform balloon atrial septostomy to ensure adequate mixing at the atrial level. Once this procedure has been performed it is likely that the patient will then tolerate discontinuing prostaglandin and surgical repair can be performed electively.

In the 1960s and early 1970s a Mustard operation was often performed at 1½ to 2 years of age or even older.[72] In these patients cardiac catheterization was usually repeated between 6 and 9 months of age, or even earlier in the patient with an associated ventricular septal defect. The main indication was concern about the development of pulmonary hypertension or the progressive nature of subpulmonic stenosis. Pulmonary hypertension, though rare in patients with transposition and an intact interventricular septum, was reported in almost every series and there was no way to determine clinically whether or not this problem was present.[73–75] When surgical repair was not performed until after 18 months to 2 years of age, it was not unusual again to perform cardiac catheterization prior to surgery. With the advent of profound hypothermia and circulatory arrest in the early 1970s, most centers began to perform a Mustard or Senning operation at a younger age.[76,77] As the age of operation became earlier in infancy, the concern about pulmonary hypertension diminished and the need for a repeat preoperative cardiac catheterization decreased as well. Currently, repeat cardiac catheterization would only be performed prior to surgical intervention in early infancy if an associated anomaly that would have an influence on the type of operation or its timing needed to be further defined. For example, if a 3 or 4 month old infant with transposition and a ventricular septal defect was being considered for surgical repair and the patient had become more cyanotic, it would be reasonable to be concerned that the patient's ventricular septal defect had become restrictive and that the left ventricular pressure was no longer at systemic level. This would have considerable influence on whether an arterial switch procedure would be performed. In addition, if the ventricular septal defect had become significantly restrictive and the patient no longer had elevation of pulmonary artery pressure, it might be worthwhile to delay surgery and perform an atrial baffle repair possibly without having to close the ventricular septal defect at all.

Postoperative Indications

In many centers, it has been the policy that patients who undergo surgical repair of complex congenital heart disease should have a postoperative cardiac catheterization.[30,78,79] Although two-dimensional and Doppler echocardiography have greatly enhanced the ability for postoperative assessment, in particular with regard to serial evaluations, cardiac catheterization remains the "gold standard" for precise hemodynamic and angiographic evaluation of the postoperative status. In view of the high incidence of electrophysiologic abnormalities, especially in patients who have undergone atrial baffle repair, intracardiac electrocardiographic assessment of sinus and atrioventricular node function has become a part of preoperative and postoperative assessment.[79,80] The postoperative cardiac catheterization in the patient who has had an atrial baffle repair will include specific procedures to evaluate for the presence or absence of pulmonary and/or systemic venous obstruction, as well as for assessment of ventricular function and the adequacy of interatrial or interventricular patches and baffles.[30,78,79] When the patient has undergone an arterial switch operation,[81] the postoperative cardiac catheterization will be used to evaluate stenosis of the anastomotic site of the great arteries, semilunar valve insufficiency, for ventricular function, and for abnormalities of the reimplanted coronary arteries.[82] These postoperative assessments will be described further in this section.

Neonatal Considerations

Cardiac catheterization in the newborn infant requires attention to a number of problems that either are not present or may be less severe outside of the neonatal period.[83] These problems include

1. Severe hypoxemia—careful monitoring of the level of systemic oxygenation is important before, during, and following cardiac catheterization. As a result of the availability prostaglandin E_1, hypoxemia is less of a problem than it has been in the past. As a general rule, a prostaglandin infusion will have been started prior to cardiac catheterization. If not, this drug should be readily available for immediate use during the procedure. An umbilical artery catheter is ideal for monitoring of systemic pressure and blood gases and should be inserted if it is not already in place at the time that the patient arrives in the cardiac catheterization laboratory.
2. Hypothermia—this is a common and potentially lethal problem in critically ill neonates especially when the infant is transported from another outlying hospital. In addition, upon

arrival at the referral center, the infant is usually subjected to multiple examinations, an electrocardiogram, a chest roentgenogram and an echocardiogram, all of which may depress further the patient's body temperature unless adequate precautionary measures are taken. It is thus essential to pay careful attention to the patient's body temperature and use an incubator or other warming device during transport. A radiant heat device should be used to maintain normothermia during examination and while performing procedures prior to cardiac catheterization. In the catheterization laboratory, the infant is placed on a radiolucent heating pad and covered with drapes and towels. Rectal temperature should be monitored continuously during the procedure.

3. Metabolic acidosis—the infant with transposition often has a compensated metabolic acidosis (normal pH with low bicarbonate and low P_{CO_2}). Since the metabolic acidosis may increase during the catheterization, arterial blood should be examined periodically for monitoring of blood gases. Bicarbonate is administered as needed.
4. Congestive heart failure—if present, this should be treated with digoxin and/or diuretics.

Route of Catheter Insertion

In the neonate less than 1 week of age with transposition of the great arteries, it is often possible to insert a soft, flexible, #5 French feeding tube into the umbilical artery. If this is successful, this line can be used to monitor systemic arterial oxygen saturation and pressure during the procedure. In an infant less than 48 to 72 hours of age, the umbilical vein can be used for both the diagnostic catheterization and balloon atrial septostomy.[84–87] Although on occasion we have been able to use the umbilical vein in patients as old as 6 or 7 days, in general the ductus venosus has closed by the third day of life. An advantage of using the umbilical venous route is that it preserves the inguinal region for future catheterizations since ileofemoral venous thrombosis is a common complication following the use of balloon catheters in the inguinal region in the newborn period.[88] A disadvantage of the umbilical approach is that it is sometimes difficult to pass the catheter from the right atrium to the right ventricle, since as the catheter passes through the ductus venosus, it is directed toward the superior portion of the foramen ovale and away from the tricuspid valve orifice.

In using the umbilical venous route, a soft #5 French feeding tube will often easily pass through the ductus venosus and into the right atrium. In contrast, it may be more difficult to pass a woven Dacron catheter or flow-directed balloon catheter through the ductus venosus. To facilitate this catheter movement, the following is recommended: the #5 French feeding tube is first inserted through a #5 or #6 French thin-walled sheath and the sheath is withdrawn back on the feeding tube as far as possible. The feeding tube is inserted into the umbilical vein and passed through the ductus venosus and well into the right atrium. The feeding tube is then held firmly in position and the sheath is advanced over it until the sheath also lies within the right atrium. The sheath is then held in position while the feeding tube is removed and the desired catheter is reinserted through it and passed into the right atrium. If a #5 French woven Dacron catheter is used, a sheath may be left in place or withdrawn onto the shaft of the catheter. If a #6 French sheath is used to enable passage of the larger diameter balloon end of a #5 French flow-directed catheter, then a mismatch will exist between the size of the catheter shaft and the internal lumen of the sheath. In this situation, it is important to withdraw the sheath out of the umbilical vein and back onto the shaft of the catheter. It can then remain in this position until it is again required for catheter exchange. It is often possible to insert a balloon septostomy catheter into the umbilical vein without the assistance of a sheath especially if a Fogarty septostomy catheter (Edwards Laboratories) is being utilized. This type of septostomy catheter has an angled tip that greatly facilitates its making the necessary bend in the ductus venosus. If another septostomy catheter is being used and cannot be passed through the ductus venosus and into the right atrium, it is possible to use the above described technique again with a #7 French sheath if this larger size is required. Another alternative is to use a #7 French sheath at the beginning of the procedure if balloon septostomy is anticipated.

If the umbilical venous route is not utilized, the percutaneous technique is used for catheter insertion into the right femoral vein. The selection of sheath will determine the type of catheter being used and the procedures to be performed. It must be remembered that when a #6 or #7 sized sheath is required for a flow-directed or balloon septostomy catheter, the shaft diameter of this catheter is usually much less than the internal diameter of the sheath required to permit passage of the larger balloon tip. It is therefore mandatory to use a sheath with a backbleed control device such as a Hemaquet (USCI Corporation) to prevent blood loss or accidental aspiration of air and resultant air embolism.

In some cases if the ductus venosus is closed and the percutaneous technique has not been successful, surgical exposure of the femoral vein is required. The site of the skin incision for cardiac catheterization in newborn infants differs from that in older infants and children in whom the saphenous bulb lies 0.5 to 1 cm caudal to the inguinal crease.[83] In newborn infants, the saphenous bulb and saphenofemoral junction lie at about the level of the inguinal crease. Although in the early years of balloon septostomy, Rashkind recommended that the incision be made 1 cm cephalad to the inguinal crease to facilitate insertion of large balloon catheters, it has generally been found that this can be accomplished using the saphenous bulb and saphenofemoral junction. Thus, the skin incision for cardiac catheterization in the newborn infant with transposition is made parallel to and at the level of the inguinal crease. The catheter is usually inserted into the saphenous bulb close to the saphenofemoral junction. The vein at this level is usually large enough to accommodate the 6.5 French tip of the balloon catheter. However, if it is found that the saphenous bulb is too small to admit the desired balloon catheter, it can be inserted into the femoral vein just caudal to the saphenofemoral junction. The saphenous bulb and its tributaries would then be left undisturbed. The femoral vein at this point is large enough and, even though it may have to be ligated after the procedure, collateral channels by way of the long saphenous vein and its branches will allow blood flow to bypass this obstruction and to enter the femoral vein downstream of it. Regardless of whether catheter insertion is near the saphenofemoral junction or in the femoral vein, careful dissection and adequate exposure of the femoral triangle, including the saphenous bulb, all its tributaries, and both proximal and distal femoral vein, are mandatory. Although this will prolong the pro-

cedure, it is time well spent since it is important to be able to control bleeding and identify the proximal and distal ends of an accidentally severed vessel. It will be easier to identify and control the end of the vessel in a well-dissected field than to start the dissection in the midst of massive bleeding from a vessel that is accidentally severed during attempts at insertion of the large end of the balloon catheter. To accomplish this, control ties are usually placed on the saphenous vein just cephalad to the entrance of the last tributaries, and on the femoral vein just proximal and distal to the site of catheter entry.[83] Care is also taken to determine if a deep perforating vessel is present in the region to be used although the site of the vessel is variable. If it is present, it must be controlled, or the femoral blood flow channeled into this vessel will cause considerable bleeding into the operative field.

Diagnostic Cardiac Catheterization

In the years prior to the availability of two-dimensional echocardiography and prostaglandin, cardiac catheterization and balloon septostomy were often performed in a critically ill and hypoxic infant. Today, the diagnosis of transposition of the great arteries is usually established by echocardiography. The infant's condition is stabilized by the administration of prostaglandin to improve systemic oxygenation and the administration of bicarbonate to reverse metabolic acidosis. Thus, baseline hemodynamic data often can be obtained prior to septostomy. If the infant's condition is stable, there is an advantage to obtaining these hemodynamic and angiographic data prior to balloon septostomy in case a problem occurs as a result of this procedure and it is not possible to obtain these data afterwards. Also if the catheterization is being performed by the cutdown technique, there is always the possibility of accidental tearing of the vessel during balloon insertion, which will then prevent reintroduction of another catheter once the balloon catheter has been removed. On the other hand, in the case of a critically ill infant, balloon septostomy should be performed as soon as possible.

Catheter Manipulation

The diagnosis of transposition of the great arteries would be suggested, but is by no means assured, as a result of passage of the catheter from the right ventricle into the aorta. This catheter pass is not diagnostic of a discordant ventriculoarterial connection since it also may be accomplished in patients with truncus arteriosus, tetralogy of Fallot, tetralogy of Fallot with pulmonary atresia, and even in a ventricular septal defect. In patients with transposition and a ventricular septal defect it is often possible to pass the catheter from the right ventricle across the ventricular septal defect and into the pulmonary artery. If the diagnosis of transposition had not been expected, as often occurred in the years before echocardiographic diagnosis of this lesion, this catheter pass might have suggested the presence of a normal ventriculoarterial connection.

The catheter is passed easily from the right atrium to the left atrium across the foramen ovale in the neonate and young infant with transposition and, of course, in those patients who have undergone balloon atrial septostomy. The foramen ovale is usually patent in the newborn with transposition and a ventricular septal defect but will usually spontaneously close during infancy unless a balloon atrial septostomy is performed. In the postoperative patient who has had an atrial baffle repair, the catheter passes easily from the inferior vena cava across the region of the baffle and into the portion of the systemic venous atrium that lies just above the mitral valve. Entry into the superior vena cava is a bit more difficult and requires that the catheter be passed along the convex lateral surface of the baffle before it enters the superior vena cava. In these postoperative patients, it is also possible to enter the pulmonary venous atrium and directly measure the pressure in the pulmonary veins. This is accomplished by passing a loop of a retrograde arterial catheter across the aortic valve into the right ventricle and then manipulating this loop in retrograde fashion across the tricuspid valve and into the pulmonary venous atrium.

In the patient with transposition, both preoperatively and following atrial baffle repair, the catheter pass from left ventricle into the pulmonary artery is difficult and requires the use of a flow-directed balloon catheter. In the past, it was possible to enter the pulmonary artery using flow-directed polyethylene tubing or following intense manipulation of a woven Dacron catheter. For the latter technique the catheter tip was positioned in the right upper pulmonary vein and the catheter advanced until a loop had formed. This loop was then backed across the mitral valve and after considerable manipulation it was often possible to pass the tip of this catheter into the pulmonary artery. These techniques are mentioned for historical interest only since the flow-directed balloon catheter is now the preferred method.

Unfortunately, in some cases, the standard flow-directed balloon catheter as it comes from the factory is too straight to pass easily across the atrial septum. Also, in the small infant, the very straight catheter often wedges in the apex of the left ventricle rather than making the necessary bend required to pass out into the pulmonary artery. We have found it extremely helpful to prepare all of our flow-directed balloon catheters, both the end-hole type and the angiographic closed end type, with a preformed curve at the tip. This is accomplished with balloon catheters in the same manner as with woven Dacron catheters. A thin curved wire is inserted into the lumen of the end-hole type catheter while a piece of small plastic tubing is passed over the angiographic balloon catheter and an appropriate curve formed with a piece of tape. These catheters are then re-sterilized and the resulting preformed curves greatly facilitate their manipulation across the atrial septum, through the left ventricle, and out into the pulmonary artery.

Oximetry

Oxygen saturation is measured in the superior vena cava, aorta, pulmonary artery, and pulmonary veins. If oxygen consumption is also measured then pulmonary and systemic blood flow as well as effective pulmonary blood flow can also be determined. The method for doing these calculations is described in the chapter on hemodynamic measurements during cardiac catheterization. A characteristic finding in the patient with transposition of the great arteries, and not usually found in patients with other abnormalities, is the presence of an oxygen saturation in the pulmonary artery that is much higher than that in the aorta. In addition, the extremely high pulmonary artery saturation found in patients with an intact interventricular septum results in a small pulmonary arteriovenous oxygen saturation difference. Thus, it must be remembered that small errors in measurement result in a large difference in the calculated pulmonary blood flow. It is also worth noting that the effective pulmonary blood flow is usually less than 20% of the

total pulmonary flow thus indicating that a relatively small percentage of the total pulmonary flow is actually participating in systemic oxygenation.[89]

Hemodynamics

In the neonate with transposition, the pressures in the ventricles and great arteries are generally equal in the first few days of life. After about 48 to 72 hours the pulmonary artery pressure begins to fall and is generally at about two-thirds of systemic level by 4 to 5 days of age and continues to fall progressively during the first month of life. This change, which parallels the decrease in pulmonary vascular resistance found in the normal newborn, occurs in the patient with transposition and an intact interventricular septum.[54] In contrast, in the patient with an associated unrestrictive ventricular septal defect, the pulmonary artery pressure remains at systemic level. This is also true when a substantial ductus arteriosus remains patent after the first few days of life. Pulmonary hypertension is of serious concern in the patient with transposition and even may be found in the patient with an intact interventricular septum.[73] If an operative repair is not performed in the early months of life, it is recommended that cardiac catheterization be performed prior to 6 months of age to measure pulmonary artery pressure. If elevated, this would be a strong indication for the patient to undergo repair, or in the presence of an associated complex ventricular septal defect, to undergo pulmonary artery banding.

An interatrial gradient is usually found prior to balloon septostomy and may be only a few mm Hg or more than 10 mm Hg. A successful balloon atrial septostomy will abolish the interatrial gradient or at most leave a residual gradient of only a few mm Hg.[90]

Subpulmonic stenosis is often found in the patient with transposition of the great arteries. When combined with an associated ventricular septal defect the subpulmonic stenosis is often severe and the patient would be classified in the complex transposition category. In the patient with an intact interventricular septum, there is usually no left ventricular outflow tract gradient in the newborn period.[30,54] However, as the left ventricular pressure falls during the first month of life, the difference between the right and left ventricular pressure results in a bowing of the interventricular septum toward the left ventricle, which produces a dynamic form of left ventricular outflow tract obstruction. It is common to find a 20 to 30 mm Hg left ventricular outflow gradient in these patients without the presence of any fixed valvar or subvalvar pulmonary stenosis.[30] If the left ventricular pressure is elevated above 40 mm Hg beyond the newborn period, it is mandatory to measure the pressure in the pulmonary artery to be certain that this elevation is the result of left ventricular outflow obstruction rather than pulmonary hypertension. If the left ventricular pressure is elevated to greater than two-thirds of the systemic level, it is important to document the cause of obstruction angiographically. Although we have seen patients with a dynamic form of outflow tract obstruction with left ventricular pressure at systemic level and little or no heart murmur, it is more common to find some form of fixed obstruction in the presence of high left ventricular outflow tract gradients.

Angiocardiography

The left ventricular angiocardiogram is diagnostic for transposition of the great arteries, in particular, when there is an intact interventricular septum (Fig. 71–19). This injection will demonstrate the discordant ventriculoarterial connection and there is no other anatomic abnormality where the pulmonary artery would be the only great vessel filled following a left ventricular injection. In contrast, although the aorta will fill from the right ventricular injection in the patient with transposition, this also occurs in patients with tetralogy of Fallot and pulmonary atresia or in truncus arteriosus. The morphologic characteristics of the ventricles are normal in the patient with transposition. Thus, the right ventricle is triangular in shape and heavily trabeculated with a vertically oriented atrioventricular valve, while the left ventricle is oval in shape with a smooth surface and an atrioventricular valve that is obliquely oriented across the outflow tract.

The origin of the left pulmonary artery from the main pulmonary artery may be at a very acute angle in the patient with transposition. The left ventricular outflow is thus preferentially directed toward the right pulmonary artery.[55] This often results in as much as two-thirds of the pulmonary artery flow going to the right and only one-third going to the left. This may be apparent either by the difference in size between the two pulmonary artery branches or by the increased opacification of the pulmonary arteries in the right lung as compared to the left.

A number of abnormalities found in association with transposition of the great arteries can be defined angiographically. A patent ductus arteriosus is commonly present in the newborn period but if it persists and is large, it may result in pulmonary hypertension and/or congestive heart failure. In addition, even a relatively small patent ductus arteriosus may mask the clinical findings of an accompanying coarctation of the aorta. A right ventricular angiocardiogram may adequately demonstrate the aorta when the interventricular septum is intact. On the other hand, in the presence of a ventricular septal defect, the left side of the heart and pulmonary artery will fill almost simultaneously and thus a selective injection in the aorta is essential. An injection in the ascending aorta with the catheter just above the aortic valve will generally not only be adequate to demonstrate the anatomy of the aortic arch, its branches, and the thoracic aorta, but will also demonstrate coronary artery anatomy in the patient being considered for an arterial switch operation. Ideally, if the total volume of contrast being used was not a concern, a selective injection in the frst portion of the descending thoracic aorta, at the site of origin of the ductus arteriosus, is best for visualization of that region.

A selective right ventricular angiocardiogram is usually performed to visualize an accompanying ventricular septal defect. In the heart with normally connected great arteries, a ventricular septal defect is best visualized in the four-chamber view (left anterior oblique with cranio-caudal angulation), or in the long axial (tilted left anterior oblique) view. Although the interventricular septum is oriented more toward the lateral plane in transposition, the ventricular septal defect will still adequately be visualized in the four-chamber view. However, on occasion it may be necessary to use more than the standard 60° of left anterior oblique. When there is pulmonary stenosis accompanying a ventricular septal defect, especially if the degree of obstruction is moderately severe and there is little or not shunt from right ventricle to left ventricle, it may be necessary to perform a selective left ventricular injection in order to visualize better the ventricular septal defect. In these cases as well the four-chamber view often is best to visualize the defect.

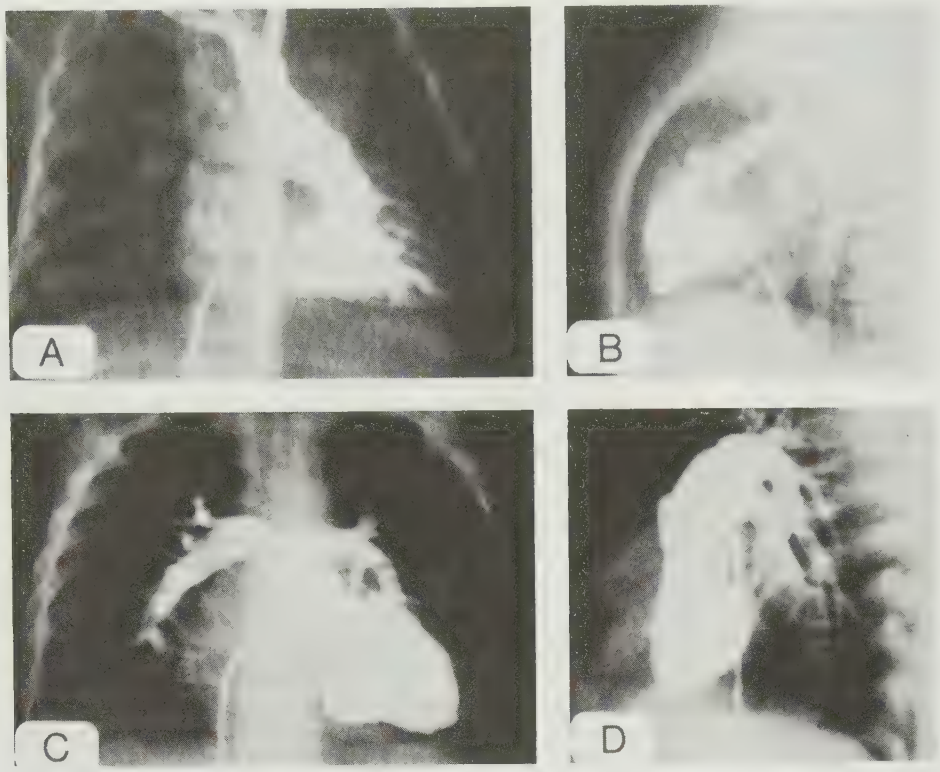

Fig. 71–19. Angiography in transposition of the great arteries. Top: right ventricular angiocardiogram in posteroanterior (A) and lateral (B) views. Bottom: Left ventricular angiocardiogram in posteroanterior (C) and lateral (D) views.

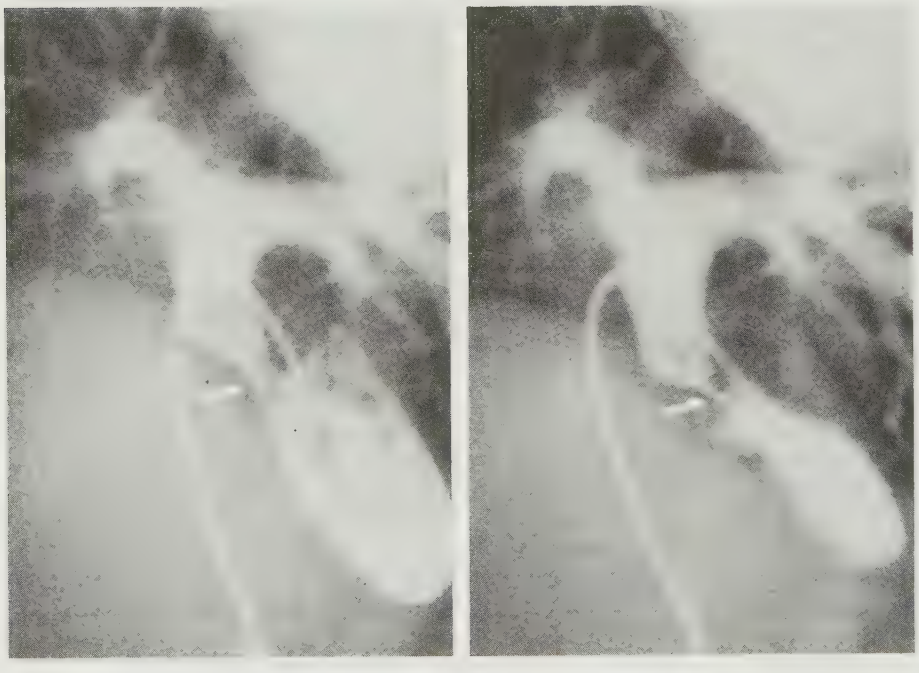

Fig. 71–20. Left ventricular outflow obstruction in transposition of the great arteries (arrows). Left: diastole, right: systole.

The anatomic cause of left ventricular outflow tract obstruction can be demonstrated by a selective left ventricular injection (Fig. 71–20). This can be accomplished with either a four-chamber or long-axial view,[36] although we generally prefer to use the four-chamber view. While mild to moderate gradients are generally produced by the dynamic form of left ventricular outflow tract obstruction, more severe obstruction with left ventricular pressure greater than two-thirds of systemic level is more often caused by a fixed obstruction. These include a discrete fibromuscular subpulmonic shelf, valvar pulmonic stenosis, pulmonary artery stenosis, and on occasion pieces of atrioventricular valve tissue. This latter form may be due to a so called "aneurysm of the ventricular septum" which is formed from pieces of redundant tricuspid valve tissue that prolapse through the ventricular septal defect into the left ventricular outflow tract (Fig. 71–21). It is also possible to have redundant portions of mitral valve tissue that behave in a similar fashion. In both cases, in particular, when this structure is related to the mitral valve, it is important to document its origin as best as possible prior to operation. Wide surgical excision of obstructing atrioventricular valve tissue may relieve the subpulmonic obstruction but may also result in significant atrioventricular valve regurgitation postoperatively.

Electrophysiologic Studies

In the majority of patients with transposition of the great arteries with intact interventricular septum, ventricular septal defect, or in complex situations, the electrical system of the heart appears to be intact prior to operation. Atrial and ventricular arrhythmias are uncommon as are disorders of atrioventricular conduction. First degree AV block is unusual while second and third degree AV block are rare preoperatively. We have performed some simple intracardiac electrophysiologic studies in preoperative patients with transposition over the last decade.[80] AH and HV intervals are usually normal as is sinus node recovery time. Stress of the AV conduction system by rapid atrial pacing has demonstrated normal function with almost all patients conducting normally at atrial pacing rates over 180 to 200 beats per minute. Similarly, other reports have described normal atrial, AV nodal, and ventricular refractory periods in preoperative patients.

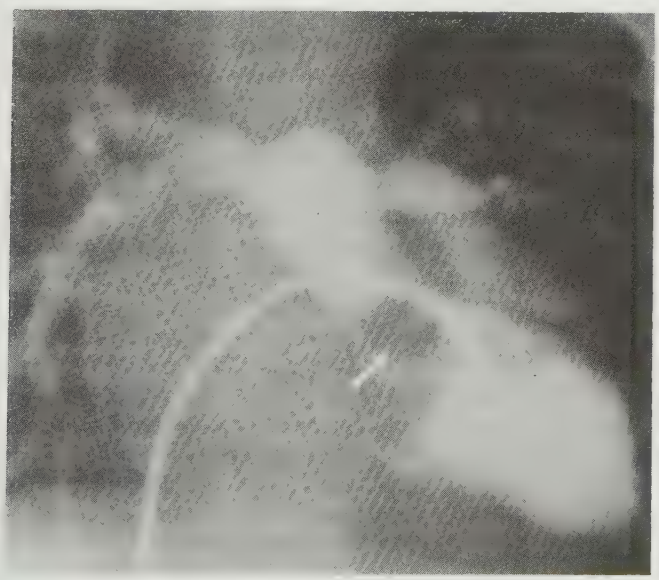

Fig. 71–21. Left ventricular angiocardiogram demonstrating an "aneurysm of the ventricular septum" (arrow) causing subpulmonic obstruction.

Although many centers began to perform the Mustard operation in the mid 1960s, it was not until the early 1970s, some 6 to 7 years later, that reports began to appear of atrial arrhythmias in longterm survivors.[78,91] It was common to see junctional rhythm with AV dissociation or junctional tachycardia in the early postoperative period. However, in most cases these abnormalities resolved and patients were thought to be in sinus rhythm. El-Said et al.[91] reported that the P-wave morphology was abnormal in postoperative patients and suggested that these were ectopic atrial foci and that a true sinus mechanism did not exist. Destruction of the sinoatrial node was demonstrated in post mortem specimens of postoperative patients and it was suggested that this, in combination with destruction of interatrial bypass pathways, was responsible for the disorders seen postoperatively.[18,91] Since that time many reports have demonstrated abnormalities on intracardiac electrophysiologic studies in patients who have had interatrial baffle repair, particularly the Mustard operation.[80,92–96] Sinus node recovery time is often abnormal and interatrial conduction may be impaired. Even patients who have an apparently normal electrocardiogram and normal 24 hour ambulatory monitoring may show abnormal sinus node function or have prolonged atrial refractory periods. Abnormal atrioventricular node function is much less common but a small percentage of patients have prolonged HV intervals, or abnormal AV node refractoriness, or in some cases third degree atrioventricular block. In general, it is more common to find these abnormalities of atrioventricular node function in patients with more complex forms of transposition who have required ventricular septal defect repair or a Rastelli operation. In contrast, atrial arrhythmias are usually found in patients who have had an atrial baffle type of repair.

CATHETER SEPTOSTOMY—TECHNICAL ASPECTS

The development of balloon atrial septostomy, by Rashkind and Miller in 1966,[10] was an important historical milestone since this was the first therapeutic interventional procedure performed in the cardiac catheterization laboratory. In the years since its introduction, balloon atrial septostomy has been successfully used worldwide and is considered to be the procedure of choice for creation of an interatrial communication in all newborn infants with transposition of the great arteries.[90,97–99] However, beyond the newborn period, it is usually difficult to create an adequate interatrial communication largely related to a thickened interatrial septum that cannot successfully be torn by a balloon. Blade atrial septostomy was developed by Park in 1975[100] to overcome the limitations of using the balloon catheter alone to try to create an interatrial communication outside the newborn period. It is now possible by using these procedures alone, or in combination, to create an interatrial communication without thoracotomy in patients at any age and even when the atrial septum is initially intact.[101–103]

Balloon Atrial Septostomy

Types of Balloon Septostomy Catheters

Early Rashkind balloon septostomy catheters were available as

either a single lumen catheter with a balloon at the tip or as a double lumen catheter with the distal end-hole connected to one lumen and a slightly more proximal side-hole connected to the balloon. These catheters had a bulky, irregular balloon section that often made it difficult to introduce the catheter into the femoral vein. The balloons did not inflate in a symmetrical, round fashion and were often "sausage shaped" and eccentrically positioned to one side of the catheter. It was not unusual to have a balloon rupture and, on at least one occasion in our series, the proximal balloon tie slipped distal to the side hole making it impossible to deflate the balloon. Over the years, the construction and quality of balloon catheters has improved considerably. The current Rashkind septostomy catheter (USCI) has a recessed balloon and can be passed through a #6 French percutaneous sheath (Fig. 71–22). The balloon has the capacity of 2 mL and its maximum inflated diameter is 12 mm. The Fogarty septostomy catheter (American Edwards Laboratory) has a 1.8 mL capacity, a slightly larger maximum inflated diameter than the Rashkind catheter, but the tip is approximately 6.5 French and therefore this catheter must be inserted through a #7 French sheath (Fig. 71–22). The Fogarty septostomy catheter is manufactured with the balloon section at approximately a 45° angle to the shaft of the catheter. Within the balloon segment the catheter tip is connected to the shaft by a coil spring device. This unique construction provides considerable flexibility of the catheter tip and makes it easy for fluid to pass in and out of the balloon. This angled, flexible catheter tip greatly facilitates passage of the catheter across the atrial septum and also makes it much easier to manipulate this catheter through the ductus venosus as compared to the straight and more rigid Rashkind type catheter. These advantages of the Fogarty catheter outweigh its disadvantages of requiring a larger size sheath or the increased difficulty of inserting it directly into a small size femoral vein. Thus, while both catheters are available in our laboratory, the Fogarty septostomy catheter is preferred whenever its use is possible. A larger balloon septostomy catheter, the Miller catheter (American Edwards Laboratory), is also available. It has a 4 mL capacity and has a maximum inflated diameter of 16 mm. This catheter also requires #7 French sheath and is most useful when a larger interatrial communication is required, such as in a patient beyond the newborn period who is undergoing a balloon atrial septostomy.

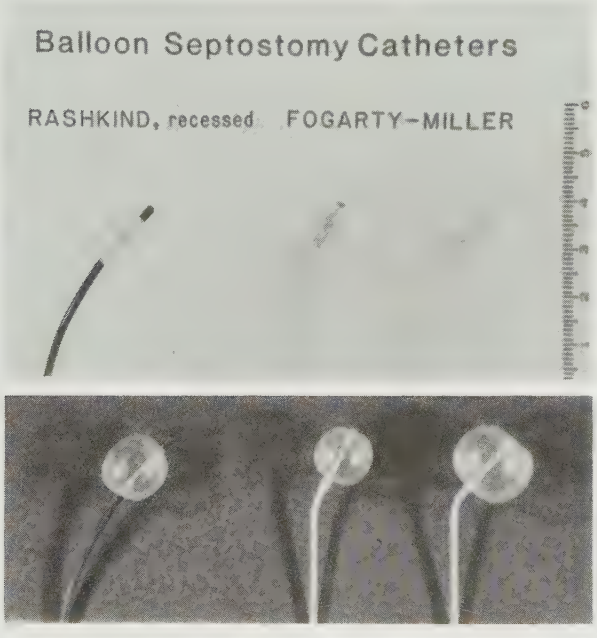

Fig. 71–22. Balloon septostomy catheters illustrating before (top) and after inflation (bottom).

Balloon Septostomy Procedure

Introduction of the balloon septostomy catheter in the inguinal region, either by the percutaneous sheath technique,[99] or if necessary by cutdown,[83] is the conventional approach. Insertion of the catheter into the umbilical vein and its passage through the liver via the ductus venosus is often possible in the infant under 3 or 4 days of age.[84–87] We would recommend an attempt to use the umbilical vein, if it is patent and accessible, in the infant under a week of age, since on occasion the ductus venosus has been found to be patent even on the sixth day of life. Although the umbilical venous route may be demonstrated angiographically to be open, there is a sharp angulation where the umbilical vein joins the ductus venosus and it may be difficult to pass the catheter across this area. However, we have found that it is generally possible to use a Fogarty balloon septostomy catheter via the umbilical venous route when it has also been possible to pass a feeding tube or a woven Dacron catheter through this area. If it is not possible to pass the balloon septostomy catheter, the necessary sized sheath can be introduced using a feeding tube by the technique that has been described above in the section on cardiac catheterization. Despite these difficulties of catheter insertion, the umbilical venous route has been as effective and safe as the femoral venous approach. It must be remembered whenever a sheath is used, regardless of whether through the umbilical vein or the femoral vein, a sheath with a backbleeding control device must be used to prevent excessive blood loss or the possibility of air aspiration into the circulation.

Once the decision has been made to proceed with balloon septostomy, a balloon septostomy catheter is inserted into the venous system, advanced to the right atrium and passed across the foramen ovale into the left atrium. It is important that the operator be certain that the catheter tip is positioned in the left atrium prior to balloon septostomy. What may appear to be a normal right-to-left atrial catheter pass in the anteroposterior view may, in fact, be a pass into the right ventricle, left ventricle, or right atrial appendage, especially when juxtaposition of the atrial appendages is present.[104,105] To avoid the potentially hazardous withdrawal of an inflated balloon from one of these areas, which might result in avulsion of an atrioventricular valve or atrial tear, the position of the catheter tip within the left atrium must be confirmed prior to balloon inflation and the septostomy procedure. This is accomplished by passing the tip of the balloon catheter past the left heart border and into a pulmonary vein. The posterior position of the catheter tip is confirmed fluoroscopically in the lateral view. If the catheter tip has been advanced into the right or left ventricle it will be directed anteriorly rather than posteriorly on the lateral view. In addition, premature ventricular contractions may be stimulated if the catheter is tapped against the heart wall. A catheter positioned in the right atrial appendage or left atrial appendage will bounce vigorously while a catheter tip appropriately posi-

tioned in the pulmonary vein will hardly move at all. Thus, a catheter tip that is beyond the left heart border and showing very little vertical movement in the anteroposterior view, which is also positioned posteriorly in the lateral view, is properly positioned in a pulmonary vein. The catheter is then withdrawn until it is inside the left heart border with the tip positioned between the left heart border and the vertebral column. The balloon is then slowly inflated while this maneuver is being monitored fluoroscopically. If the balloon is difficult to inflate or is inflating in an elongated rather than a round fashion, this may indicate that it is positioned in the pulmonary vein. If this occurs the balloon must be deflated, the catheter withdrawn slightly, and then inflation again attempted. Careful attention must be paid to this maneuver since full inflation of the ballon in a pulmonary vein or the left atrial appendage may result in inadvertent rupture of these structures.

It is also possible to use two-dimensional echocardiography to determine that the catheter is appropriately positioned within the left atrium. Some centers have recommended echocardiography as the sole imaging method for balloon atrial septostomy in the newborn nursery or intensive care unit, while others have suggested combined echocardiographic and fluoroscopic guidance in the cardiac catheterization laboratory.[69–71] Although each of these methods has its advantages and disadvantages, it is still generally preferred to perform balloon atrial septostomy in the cardiac catheterization laboratory. Regardless of which imaging technique is utilized, the operator must pay careful attention to details such as the position of the catheter tip within the left atrium and initial slow inflation of the balloon to avoid injury.

As the balloon is inflated under direct vision, either by fluoroscopy or echocardiography, the catheter is slightly withdrawn to ensure that the balloon is being inflated within the left atrium. The balloon should be inflated to the maximum desired diameter for the initial withdrawal. In the newborn, the appropriate balloon diameter is approximately the same size as the side-to-side width of the patient's vertebral column. This is generally achieved by using the recommended maximum inflation volume. For example, with a #5 French Fogarty septostomy catheter, an inflation volume of 1.8 mL results in a balloon diameter of about 15 mm. In smaller neonates, including premature infants, the desired inflation diameter of the balloon occurs with less volume. It has been suggested by some investigators that an initial septostomy be performed with a less-than-maximum balloon diameter, with the balloon progressively inflated for successive withdrawals. This technique runs the risk of simply stretching the interatrial communication, rather than tearing of the valve flap of the foramen ovale, which is the desired result. It is therefore recommended that the maximum desired balloon inflation diameter be used for the initial, as well as successive, withdrawals.

As the balloon is inflated within the left atrium, it is generally withdrawn against the atrial septum until the appropriate diameter has been achieved. The catheter is then withdrawn from the left atrium to the right atrium with a rapid, short, jerking motion. This maneuver will tear the valve of the foramen ovale and it is again important to stress that this tear should occur on the first withdrawal (Fig. 71–23). A few additional withdrawals are often performed and may slightly extend the tear that was started with the first pullback.

The early results of balloon atrial septostomy are assessed on the basis of changes demonstrated in the catheterization laboratory, echocardiography and, of course, clinical improvement. It is common to find a pressure gradient between the left and right atrium before balloon septostomy and this gradient should be abolished or minimized by the procedure (Fig. 71–24). A satisfactory balloon septostomy should result also in either a rise in systemic atrial oxygen saturation of 10%, or an arterial oxygen saturation of greater than 60%.[97,98] Improvement in systemic arterial oxygen saturation is most pronounced in the patient with transposition and an intact interventricular septum. In the presence of a ventricular septal defect, the systemic arterial oxygen saturation may be high before septostomy and thus it is possible that little or no change may occur following the procedure. Although an oxygen saturation of 60% of greater is a criterion for an adequate balloon septostomy result, a saturation below this level may be found in patients with adequate palliation who do not require additional surgical intervention.[106] Echocardiography is extremely valuable to assess the result of balloon atrial septostomy. The atrial septum is easily visualized from the subcostal approach and an adequate balloon septostomy should result in an atrial septal communication that measures at least 8 mm in diameter echocardiographically (see Fig. 71–14).

There is a small group of patients who do not show clinical improvement despite having had an apparently successful balloon septostomy as evidenced by a reduction or elimination of the interatrial gradient and echocardiographic demonstration of an adequate atrial septal opening. Some of these patients will improve in the 48 to 72 hours following septostomy. The remaining small number of patients have some deficiency in atrial mixing that is not readily explained but is thought to be due to preferential flow of the pulmonary venous return toward the mitral valve. In some cases this may be improved by volume expansion and continued prostaglandin administration. Those patients with continued poor atrial mixing despite these measures may not be improved further even by blade septostomy or by Blalock-Hanlon atrial septectomy. These patients usually required early operation which, in the past, was an atrial baffle procedure.

Blade Atrial Septostomy

Although the initial balloon septostomy may appear to be successful in the vast majority of patients with transposition of the great arteries, the interatrial communication may subsequently be found to be inadequate in up to 20% of cases. Repeat balloon septostomy, or even a primary procedure toward the end of the first month of life, is generally unsuccessful largely due to a thickened interatrial septum which cannot be torn effectively by a balloon catheter.[97,98] Blade atrial septostomy was developed to overcome this limitation of a balloon septostomy. The clinical use of blade septostomy in a limited number of patients was first reported by Park et al. in 1978.[101] An extensive collaborative study among multiple centers was reported in 1982 and established the efficacy and safety of this procedure.[102] Blade atrial septostomy is now widely utilized both in the United States and abroad in the management of patients with transposition as well as a wide variety of other disorders.[103]

Procedure and Technique

The blade septostomy catheter is currently available (Cook, Inc.) in 9.4 mm, 13.4 mm, and 20 mm lengths. The smaller catheter is generally adequate for use in infants while the larger

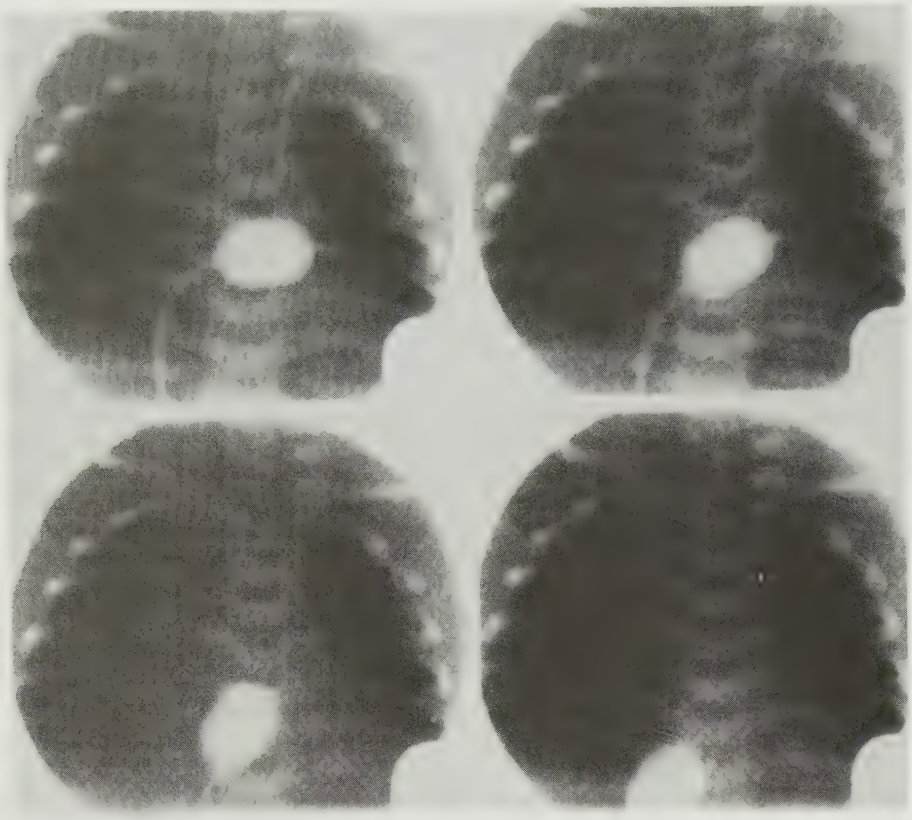

Fig. 71–23. Consecutive cineangiogram frames demonstrating balloon septostomy; speed of cineangiogram, 60 frames/second.

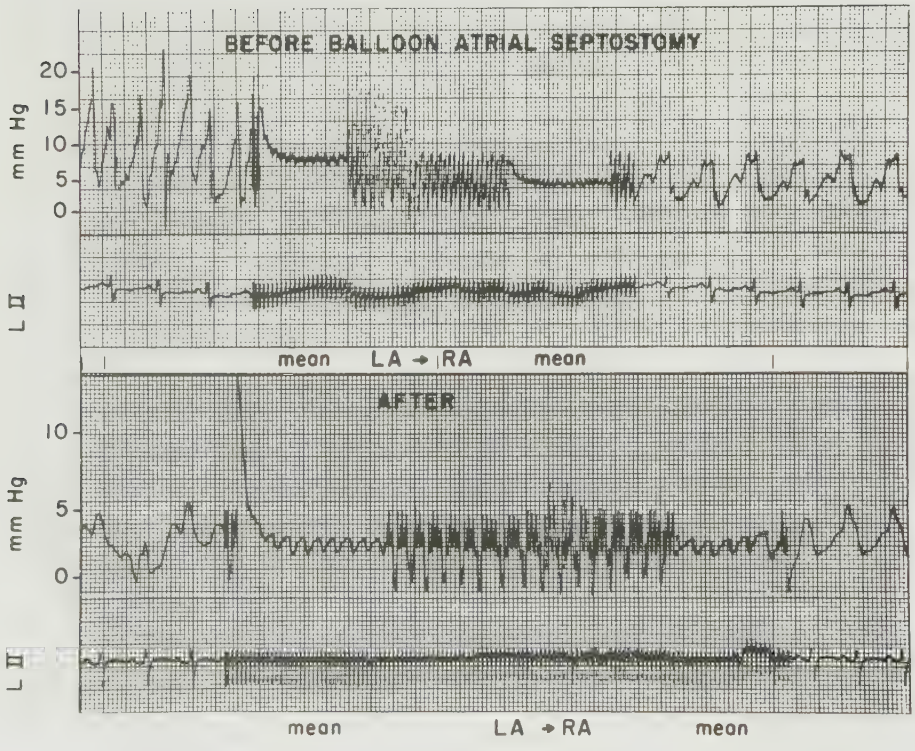

Fig. 71–24. Left to right atrium pressure withdrawal record before and after balloon septostomy in a patient with transposition of the great arteries.

catheters are used in older patients in whom a larger interatrial communication is required. The blade catheter has a long straight metal component at the tip that is angulated at about 25° to the catheter shaft (Fig. 71–25). Unfortunately, this degree of angulation is still not sufficient to permit easy passage of the catheter tip across the atrial septum into the left atrium in many cases. This is particularly true in the patient with a small left atrium or when there is an unusual location of the interatrial communication. It is thus recommended that a long percutaneous sheath (Mullins transseptal sheath, USCI) be utilized to introduce the catheter tip into the left atrium (Fig. 71–26). Prior to use, the length of the sheath should be compared to that of the balloon and blade catheters to ensure that the working portion of the catheter will protrude beyond the distal end of the sheath. If the sheath is found to be too long, it can be cut back to an appropriate size using a scalpel blade. To permit easy manipulation of the blade catheter within the sheath, a #7 French sheath is recommended for the blade septostomy procedure. This will also eliminate the need to change the sheath if a Fogarty catheter is used for the subsequent balloon septostomy. In performing blade and balloon septostomy, it is preferable to use a sheath with a side port and a backbleeding control device. This will permit intermittent or slow continuous infusion of heparinized flushing solution through the side port of the sheath during the procedure. This infusion, in combination with the backbleed control mechanism, will prevent either the possibility of air aspiration due to air entrapment during catheter exchange, excessive blood loss, or thrombus formation within the sheath.

The sheath is initially introduced into the right atrium using a guidewire and its long dilator (Fig. 71–26:1).[103] The guidewire and dilator are removed and a regular woven Dacron catheter is introduced into the sheath and passed into the left atrium (Fig. 71–26:2). The sheath is then advanced over the catheter into the left atrium and the catheter is withdrawn, thus leaving the tip of the sheath within the left atrium (Fig. 71–26:3). The blade septostomy catheter is then passed through the sheath into the left atrium (Fig. 71–26:4). The sheath is withdrawn while the tip of the blade catheter remains within the left atrium. The blade component is opened and the catheter rotated in a counterclockwise direction so that the blade faces anteriorly in the lateral fluoroscopic view. The catheter is then slowly withdrawn and a gentle but steady force is maintained until a sudden loss of resistance is felt and the catheter passes into the right atrium (Fig. 71–26:5). If the atrial septum is thickened and unusually tough, the blade may reach to the level of the diaphragm before it "pops free." It is important to remember that septostomy with a blade catheter is performed using a slow, steady withdrawal as compared to the rapid, sudden jerking motion of balloon atrial septostomy. Blade septostomy is safely performed as long as resistance is met in the usual mid-portion of the atrium and there is no loss of resistance or sudden change of angulation during slow catheter withdrawal. Several passes of the blade catheter across the atrial septum should be performed with a slightly different angulation each time to ensure an adequate tear. After this has been accomplished, the blade catheter is withdrawn and a balloon septostomy catheter is then introduced into the left atrium (Fig. 71–26:7). Balloon septostomy is performed in the usual fashion, thus further enlarging the newly created interartial communication (Fig. 71–26:8). It is important to emphasize that, during blade or balloon septostomy, the sheath and the septostomy catheter must be pulled together in unison so that the distal tip of the long sheath is not damaged during the septostomy procedure.

Malfunction of the blade septostomy catheter has occurred occasionally. This has usually been because of difficulty in retracting the blade component back within the catheter lumen and is probably related to opening the blade section beyond the recommended maximum angle. To avoid this problem, careful inspection of the blade septostomy catheter and trial attempts at opening the blade and evaluating the maximum angle are essential prior to introduction of the catheter into the patient. Also, intermittent or slow continuous infusion of heparinized fluid through the side port of the blade catheter will prevent clot formation, a problem that might interfere with retraction of the blade component into the catheter lumen.

MANAGEMENT OF THE PATIENT WITH TRANSPOSITION OF THE GREAT ARTERIES

The introduction of balloon atrial septostomy in the mid-1960s was the single most important factor to influence the survival of the infant with transposition of the great arteries. Many other milestones have occurred over the four decades since the first systemic to pulmonary artery anastomoses were developed (Table 71–1). Over the years as these various improvements in management became available, the age at which repair of transposition is performed has become progressively younger. Today, most centers would attempt repair of transposition in the early months of life. This change in management from an invariably fatal congenital malformation for which nothing could be done, to the current era of arterial switch procedures and neonatal repair, is best demonstrated by examining the natural history of patients with this anomaly and how it has been modified by the advances of medical and surgical therapy over the last four decades.

Natural History and its Modification by Therapy

To best assess the effect of medical and surgical management on the natural history of transposition of the great arteries, it is worthwhile to consider the morbidity and mortality of infants in

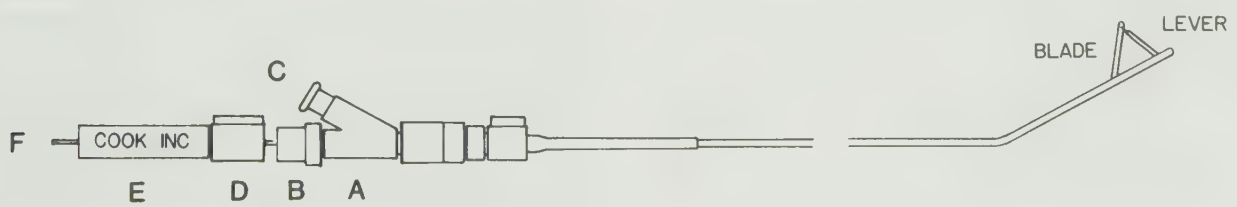

Fig. 71–25. Diagram of a blade septostomy catheter.

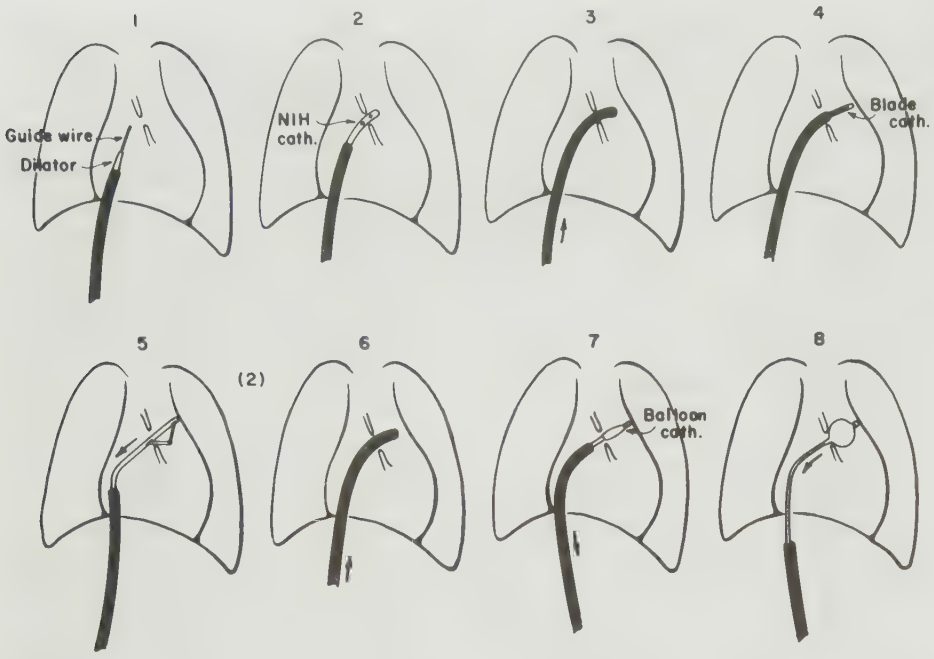

Fig. 71–26. Diagrams illustrating the use of a long sheath for blade and balloon atrial septostomy (see text for description of procedure).

the first year of life. The last four decades span major eras in the management of infants with transposition. The first period, prior to 1950, is an era during which surgical therapy essentially was not available. Although palliative surgical options were first made available in the late 1940s,[107,108] very few centers had surgeons trained in these techniques and thus management was generally nonsurgical, and patients with this diagnosis usually died. In two large series reported by Liebman[3] and by Shaher,[5] about 90% of patients with transposition and intact interventricular septum died in the first year of life. These patients usually succumbed to the effects of hypoxemia and congestive heart failure. Patients with transposition and a ventricular septal defect usually lived somewhat longer since they have less problems with severe hypoxemia. However, mortality was high due to congestive heart failure. A few patients did survive when their pulmonary blood flow became reduced to more tolerable levels by the development of pulmonary vascular obstructive disease. Patients with complex transposition, those with a ventricular septal defect and accompanying pulmonary stenosis, had the best survival since excessive pulmonary blood flow was not a problem, and those with moderate pulmonary stenosis did not require surgery. Patients with severe pulmonary stenosis or pulmonary atresia usually died, but some were salvaged by systemic-to-pulmonary artery anastomoses toward the end of that period.

Table 71–1. Chronology of Management of Transposition of the Great Arteries

Presurgical: Prior to 1950
1945: Blalock-Taussig[107] and Potts[108] anastomoses
Palliative surgical: 1950–1963
1950: Blalock-Hanlon atrial septectomy[7]
1952: Pulmonary artery banding[109]
1956: Baffes procedure[112]
1959: Senning operation[8]
1962: Waterston/Cooley anastomosis[110,111]
Surgical repair: 1964–1973
1964: Mustard operation[9]
1966: Rashkind balloon septostomy[10]
1969: Rastelli operation[113]
1970–1973: Profound hyperthermia[114,115]
Repair during infancy: 1974–1983
1975: Park blade septostomy[100]
1976: Jatene arterial switch operation[81]
1977: Prostaglandin E_1[116,117]
1977: Senning operation (revival)[118]
Current era of management: 1984–Present
Atrial baffle vs. arterial switch

The natural history of transposition of the great arteries was gradually modified during the period from 1950 to 1963. During this pre-repair era, there was a proliferation of cardiac surgical centers. The widespread availability of the Blalock-Hanlon atrial septectomy,[7] pulmonary artery banding,[109] and systemic-to-pulmonary artery anastomoses[107,108,110,111] resulted in a considerable increase in the survival of patients with transposition. The Baffes procedure, described in 1956, consisted of a transfer of the inferior vena cava to the left atrium and the right-sided pulmonary veins to the right atrium.[112] This was attempted by some but was largely unsuccessful. Although Senning's operation had been described in 1959, it also was generally unsuccessful and was thus abandoned.[8] The next era of management from 1964 through 1973, marked the introduction of balloon atrial septostomy,[10] Mustard's operation,[9] and the Rastelli procedure.[113] These procedures dramatically altered the survival and prognosis of patients with transposition, especially those with an intact interventricular septum. This resulted in a much more aggressive approach to the management of the newborn and small infant with this disorder.

In the fourth period, 1974 through 1983, repair of transposition during the first year of life became common through the widespread use of profound hypothermia and circulatory arrest.[114,115] The introduction of prostaglandin E_1 provided a pharmacologic means of improving oxygenation of newborns until palliative or

definitive procedures could be performed.[116,117] The development of blade atrial septostomy[100] and the arterial switch[81] procedures during this period further influenced the already modified natural history of patients with this disorder. In the early 1980s, the previously abandoned Senning operation gained popularity and most centers began to use it in preference to the Mustard operation.[118]

Although the major advances in therapy have been outlined above, it must be remembered that many improvements in other areas had a profound influence on the management, morbidity, and mortality of infants with transposition. For example, in the early 1970s it was recognized that in addition to polycythemia, anemia or relative anemia were also important factors in the management of the hypoxic infant.[119,120] Around this time, the development of intensive care units together with the specialty of critical care medicine was initiated. Both of these factors improved the survival of extremely ill patients before and after palliative or reparative procedures. Critical care facilities have continued to improve during the last decade and many new pharmacologic agents have been introduced. A striking improvement in emergency transport facilities has occurred so that helicopter transport is now available in most tertiary referral centers. A team of skilled physicians and nurses can now be sent to outlying areas to provide rapid and stable transport of critically ill patients.

Despite these many advances in medical and surgical management, the modified natural history of the infant with transposition still included preoperative morbidity due to hypoxia and polycythema, or problems with pulmonary vascular obstructive disease. Postoperative problems included left ventricular outflow obstruction, right ventricular dysfunction, baffle obstruction, and arrhythmias. As a result of these ongoing problems, many centers began to look for a way to avoid these complications and thus entered the era of the arterial switch repair.

Prior to a discussion of the results of procedures available for palliation in the cardiac catheterization laboratory, or for surgical management, it is appropriate to consider some of the complications that have led to the desire to repair the infant with transposition of the great arteries as early in life as possible.

Hypoxia and Polycythemia

In the years prior to the repair of transposition during infancy, a post-balloon septostomy systemic arterial oxygen saturation of 60% or greater was considered to be an adequate result of palliative therapy.[97,98,106] This systemic desaturation did not seem to have a great effect on growth and development although these patients certainly did have less exercise capacity and stamina than their normal healthy siblings or peers. Some investigators have found that patients with transposition, even those with apparently adequate palliation, have delayed growth as compared to their normal peers. In addition, although most patients with transposition have normal intellectual and motor development, some do not.[121] However, it is extremely difficult to determine the specific etiology of developmental problems in patients with transposition who not only are cyanotic but also undergo multiple cardiovascular procedures. It is possible that this is related to the cyanosis. However, it may be related instead to the surgical procedures, to the timing of these procedures, or possibly even to the psychosocial abnormalities that are known to occur in this group of patients.

Polycythemia is a major physiologic consequence of the presence of hypoxemia. In general, patients with transposition and adequate palliation have an increased red blood cell count and a hemoglobin that is between 17 and 19 g/dL. This corresponds to a hematocrit of between 50 and 57%. When the hematocrit is in this range, the increased number of red blood cells is sufficient to provide adequate peripheral oxygen delivery while it is not so high as to produce the serious side effects of polycythemia. However, when the hematocrit is above 60% the viscosity of blood increases geometrically for each linear increase in the percent hematocrit. This tends to produce a substantial increase in viscosity especially when the hematocrit is over 65%.[122] This increased viscosity results in peripheral sludging of blood and places the patient at greater risk for having the neurological complications that will be described below. Another important complication of high hematocrit and high blood viscosity is the alteration of clotting factors that occurs in these patients.[123,124] When the hematocrit is 65% or higher, there is an alteration of the coagulation status with increased prothrombin time and low platelets, fibrinogen, and other coagulation factors. This most likely occurs as a result of a subclinical consumption coagulopathy.[124,125] Although this altered coagulation state is usually of little consequence, it is a serious problem for the patient who is about to undergo open heart surgery. Thus, when a polycythemic patient with a hematocrit over 60% is about to undergo surgical repair, it is important to check the patient's coagulation profile about a month prior to operation. If it is found to be abnormal, then phlebotomy and an exchange with a plasma substitute is recommended to be performed approximately a week to 10 days prior to operation. Reduction of the hematocrit below 60% serves to improve the cardiovascular status,[126] reduce peripheral sludging, and will improve the patient's coagulation status thus minimizing the risk of bleeding diathesis postoperatively.[127]

Neurologic Complications

Patients with transposition of the great arteries, especially those with marked polycythemia, may have a wide range of neurologic problems, some of which are readily reversible and others with permanent residua.[119,120] Headaches are a common complaint of patients with polycythemia especially when the hematocrit is over 65%. These are probably related to the sludging of blood in the capillary circulation of the brain and these symptoms are readily reversed following phlebotomy procedures. Delayed intellectual and/or motor development and seizures occur in patients with transposition of the great arteries.[121] It is possible that these problems are related to the profound systemic hypoxemia that many of these patients had during the neonatal period or early infancy.[128] However, it must be remembered that in transposition as in other patients with cyanotic congenital heart disease, there is a direct route from the systemic venous circulation to the systemic arterial circulation and thereby to the brain. Spontaneous intravascular thromboses, either arterial or venous, can occur in the presence of severe polycythemia. Thus, small intracerebral vessel thrombosis, or peripheral venous thrombosis with systemic arterial embolization, can occur in the absence of an apparent major clinical event and yet result in these neurologic abnormalities. In the same respect, these patients may have inadvertent systemic arterial embolization during one of their multiple cardiac catheterizations or surgical procedures. Cerebrovascular accidents, which are more severe and permanent neurological complications, may have the

same underlying mechanism. These are often temporally related to procedures although as many as 50% occur spontaneously.[129]

Although the majority of these complications are related to procedures or occur in polycythemic patients, anemia may also be a factor.[119,120] While a hemoglobin concentration of 12 to 14 g/dL is normal for a noncyanotic patient, this level of hemoglobin, or lower, is a significant relative anemia for a patient with transposition who is hypoxemic. It has been our experience and that of others that relative anemia in a cyanotic patient is as much a risk factor for cerebrovascular accident as is severe polycythemia. Thus, patients at either extreme, with a hemoglobin below 15 grams or above 20 and corresponding hematocrit below 45% or above 60%, are at risk for the development of neurologic complications especially during infectious illnesses. Careful attention therefore must be paid to and appropriate management instituted for not only polycythemia but also relative anemia. If a patient with transposition and hypoxemia is found to have a hemoglobin less than about 16 g/dL and a corresponding hematocrit of about 50%, supplemental oral iron therapy should be instituted to raise the hemoglobin and hematocrit to what is considered an appropriate level for that patient's degree of cyanosis and hypoxemia.

Pulmonary Vascular Obstructive Disease

Patients with other forms of cyanotic congenital heart disease generally have reduced pulmonary blood flow and therefore are not at risk for pulmonary vascular disease. Patients with transposition of the great arteries have increased pulmonary blood flow, yet have cyanosis as a result of poor mixing between the two separate parallel circulations. It has been well documented that patients with transposition and an additional shunt lesion, such as a ventricular septal defect or large patent ductus arteriosus, are at risk for developing this complication.[73–75] Furthermore, this problem occurs even in patients with transposition and an intact interventricular septum. It is possible that this predisposition to the development of pulmonary vascular disease in patients with transposition is somehow related to a combination of a number of factors. These include the large amount of pulmonary blood flow, the increased shear forces on the walls of the pulmonary arterioles caused by the polycythemia, the large additional systemic to pulmonary collateral flow seen in some patients, or some other unknown factor. In most cases where pulmonary vascular disease has occurred, the etiology is unclear. In the past, when repair of transposition was often delayed until the end of the first year of life or later, it was important to measure the pulmonary artery pressure in all patients with this abnormality at around 6 months of age. With the advent of surgery during infancy, concern about pulmonary hypertension now usually only remains in patients who have undergone banding of the pulmonary artery or who have not had repair of their anomaly by 6 months of age. Although it is uncommon today, there are some patients with transposition and a ventricular septal defect who have already developed pulmonary vascular disease for whom effective palliation can be achieved by performing an atrial baffle repair without closure of the ventricular septal defect.[130–132]

Catheter Septostomy—Results

Balloon atrial septostomy was the first interventional procedure used in the cardiac catheterization laboratory. It was extremely successful in providing immediate palliation for the patient with transposition of the great arteries. With widespread availability of balloon catheters by the late 1960s and early 1970s and the dissemination of information about the appropriate methods to be employed in performing this procedure, successful initial palliation was achieved in over 85% of patients.[90,97] Effective longterm palliation for as long as 2 or 3 years was possible for 65 to 75% of patients who underwent balloon atrial septostomy during infancy.[133] Until the development of blade atrial septostomy by Park in 1975[100] no other nonsurgical option was available for the approximately 25% of patients in whom balloon atrial septostomy was not effective either initially or subsequently during infancy. In an extensive collaborative study reported in 1982,[102] about 80% of this group of patients who required additional palliation by blade septostomy during infancy and childhood had an adequate result.

Despite the widespread use and unquestionable benefit of balloon and blade atrial septostomy, complications of these procedures have taken their toll. Most series describing the results of balloon septostomy from the 1960s and 1970s reported an occasional complication due to tears of myocardial or vascular structures, or injury to the mitral or tricuspid valve during the procedure. Today, with careful attention to detail, biplane fluoroscopic determination of catheter position and/or echocardiographic guidance, these complications of balloon atrial septostomy have largely been eliminated. Myocardial perforation or tear has also been reported in a few cases during blade septostomy.[102] These occurred during the early experience with this procedure and subsequent modifications of the blade catheter and careful use of the recommended procedures should minimize the likelihood of future occurrences. Major neurologic complications have occurred during or shortly following both balloon and blade septostomy procedures.[102,103,129] In the case of balloon septostomy, some of these were related to balloon rupture and embolization of balloon fragments. This problem has been largely eliminated due to improved materials and techniques of catheter design. In addition, careful evacuation of air from the balloon prior to catheter insertion and subsequent inflation in the patient, will minimize the possibility of air embolism should rupture of the balloon occur during septostomy.

Other causes of cerebrovascular accident occurring during or after cardiac catheterization and balloon or blade septostomy, include profound hypoxemia before or during the procedure, excessive blood loss, aspiration of air through a sheath into the venous system, or clot formation and systemic embolization. Profound hypoxemia is less of a problem today because of the use of prostaglandin E_1 in the neonatal period. Excessive blood loss due to tearing of femoral venous structures was a problem in the 1960s and early 1970s when catheters were inserted by the cutdown method. Blood loss was also a problem initially, using the percutaneous technique, since the internal diameter of the sheath required for balloon or blade insertion was much larger than the diameter of the catheter shaft. This not only resulted in the problems with excessive blood loss but also had the potential for allowing introduction of air through the sheath during the procedure. Today, most centers would insert these catheters by percutaneous technique wherever possible. The use of a sheath with a side port and a backbleeding control device is essential to prevent these complications.

Palliative Surgical Procedures

The era of surgical management of transposition of the great arteries began in 1950 with the description of closed atrial septectomy by Blalock and Hanlon[7] and pulmonary artery banding by Muller and Dammann.[109] Although the Blalock-Hanlon technique provided effective palliation for patients with transposition, especially those with an intact interventricular septum, the mortality from this procedure was high and ranged from a low of 20% to as high as 80%.[134–137] After the development of balloon septostomy, surgical septectomy was still used in patients in whom adequate palliation could not be achieved with the balloon catheter. The need for surgical palliation of transposition decreased considerably as more centers began to use profound hypothermia and circulatory arrest for repair of this lesion during infancy. Thus, by the early 1980s it was rare for a Blalock-Hanlon atrial septectomy to be performed in most institutions.

Pulmonary artery banding is used to reduce pulmonary blood flow in a patient wth transposition and a ventricular septal defect.[133] From 1950 through 1965 this was the only means of treatment of patients with this combination. Those who did not have this procedure either died or developed pulmonary vascular disease. Even during the decade following the description of the Mustard operation, repair was generally performed after 2 years of age. Thus, pulmonary artery banding was required during infancy for patients with an associated ventricular septal defect. In most patients, successful palliation was achieved with pulmonary artery banding alone or in combination with balloon septostomy or surgical atrial septectomy.[138] After it became possible to repair transposition of the great arteries during infancy, most centers preferred to perform a primary repair whenever possible rather than to perform pulmonary artery banding during infancy followed by repair at an older age.[79,139] Exceptions to this occurred in very small infants or in patients with associated multiple ventricular septal defects.

The arterial switch repair, described by Jatene in 1975, requires the left ventricle to function as the systemic ventricle postoperatively.[81] In order for this operation to be successful, the left ventricle needs to be ''prepared'' for systemic pressure.[140] This is not a problem in the neonatal period since the left ventricle has functioned against systemic pressure and resistance during fetal life. However, after 3 or 4 weeks of life, the left ventricle will no longer be able to function as the systemic ventricle unless it continues to face systemic pressure after the neonatal period. In patients with a ventricular septal defect and equal pressures in the right and left ventricle, an arterial switch procedure therefore is still possible later during infancy. In an infant, it is possible either to perform a pulmonary artery banding and consider an atrial baffle or arterial switch repair later during infancy or childhood, or to perform a primary repair early in infancy. In some centers pulmonary artery banding has also been used to ''prepare'' the left ventricle in patients with transposition and an intact interventricular septum who are beyond the neonatal period. In these patients, pulmonary artery banding is performed to raise the left ventricular pressure near to systemic level for a few months before arterial switch repair is performed.[141]

Systemic-to-Pulmonary Artery Anastomoses

The Blalock-Taussig anastomosis described in 1945,[107] or more recently its modified form using the Gore-Tex interposition graft between the subclavian and pulmonary arteries,[142] are the procedures of choice in infants with transposition and significant left ventricular outflow tract obstruction. In general, these are patients in the complex transposition category who have an associated ventricular septal defect and pulmonary stenosis. However, on occasion, a systemic-to-pulmonary artery anastomosis is effective even in a patient with transposition, an intact interventricular septum, and severe left ventricular outflow tract obstruction. Although other anastomoses, such as those described by Waterston,[110] Cooley,[111] and Potts,[108] have been used in the past, problems of pulmonary hypertension, kinking of the pulmonary arteries, and difficulties of takedown at the time of repair have made these anastomoses less favored than the previously mentioned subclavian artery procedures. In general, these procedures have been quite successful in providing effective longterm palliation for patients in the complex transposition category.

Atrial Baffle Procedures

A number of different types of partial and complete atrial redirection operations, including the Senning operation,[8] were suggested but had little success prior to the description of the atrial baffle repair by Mustard in 1964.[9] Subsequently, this technique was the only procedure used by most centers for the repair of transposition until the early 1980s when it became popular instead to use the Senning operation.[118] The goal of both the Mustard and the Senning atrial baffle procedures is to redirect the venous inflow to the heart so that the pulmonary venous drainage is channeled to the tricuspid valve and the systemic circulation, while the systemic venous drainage is channeled to the mitral valve and the pulmonary circulation. In the Mustard operation, an incision is made in the right atrium (Fig. 71–27A) and the atrial septum is then excised widely (Fig. 71–27B and C). A baffle of either autologous pericardium or synthetic material is used to partition the atrium. The baffle is sutured to the left side of the pulmonary veins and then around the vena caval orifices (Fig. 71–27D). This will direct the systemic venous inflow on the left side of the baffle and into the mitral valve. Pulmonary venous drainage will pass around the baffle and into the tricuspid valve. A patch is usually used to enlarge the new pulmonary venous atrium at the end of the procedure (Fig. 71–27E).

The Senning operation takes a different approach to provide similar partitioning. In contrast to the Mustard operation where the atrial septum is excised, the Senning procedure uses a flap of atrial septum to form part of the baffle (Fig. 71–28). After an initial atrial incision is made, (Fig. 71–28A) the atrial septum is detached with a U-shaped incision, along the anterior-superior margin (Fig. 71–28B). The flap of interatrial septum is sutured to the posterior left atrial wall so as to include the pulmonary veins behind this newly moved septal flap (Fig. 71–28C). If the flap is insufficient due to a large atrial septal defect, a patch of synthetic material is usually added. Then, another incision is made in the wall of the left atrium parallel to the initial right atrial incision but just to the left of the interatrial septum (Fig. 71–28C). The medial flap of atrial wall is then sutured to the interior of the atrium along the free margin of the previous incision in the atrial septum (Fig. 71–28D). This will serve to direct the systemic venous return to the left atrium. The remaining portion of right atrial wall is then pulled over this internalized flap and sutured to the posterior left atrium thus forming the new pulmonary venous atrium (Fig. 71–28E). An additional patch is frequently used to

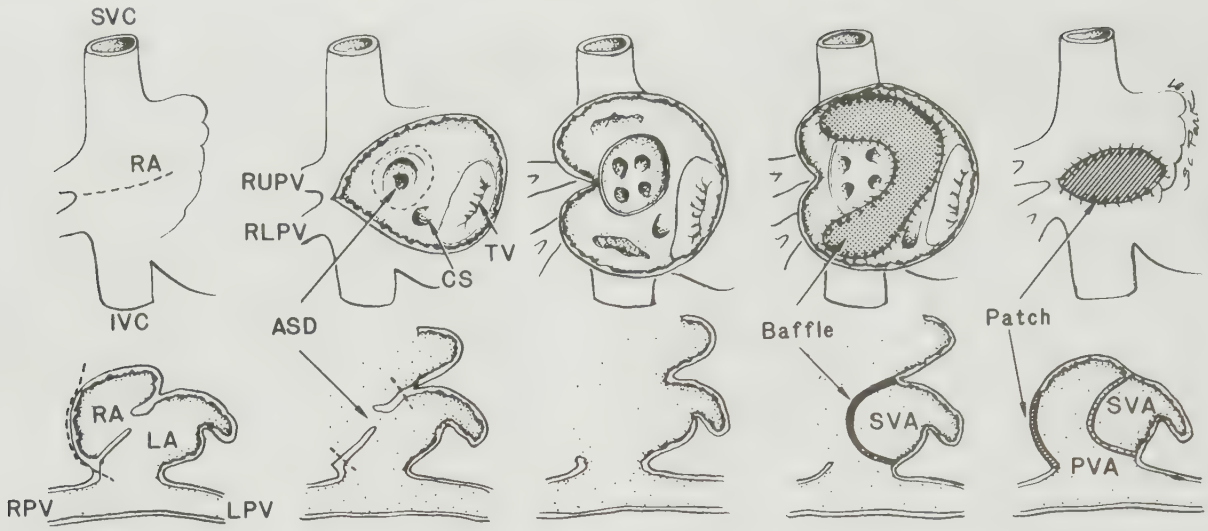

Fig. 71–27. Diagram illustrating the Mustard operation (see text). Top: surgical view of the repair through right atrium. Bottom: cross-section view of each sequence of the repair. ASD = atrial septal defect, RLPV = right lower pulmonary vein, CS = coronary sinus, RPV = right pulmonary vein, IVC = inferior vena cava, RUPV = right upper pulmonary vein, LA = left atrium, SVA = systemic venous atrium, LPV = left pulmonary vein, SVC = superior vena cava, PVA = pulmonary venous atrium, TV = tricuspid valve, RA = right atrium.

enlarge this new pulmonary venous atrium. These multiple infoldings of tissue flaps appear to be quite complex and are difficult to visualize. This led to the abandoning of the Senning procedure in the mid 1960s in favor of the simpler Mustard operation. However, despite these apparent difficulties, our surgical colleagues now tell us that the Senning procedure is actually easier to perform in infants and small children.

In the years before the use of profound hypothermia and circulatory arrest, the Mustard procedure was generally performed between 1 and 3 years of age with over 80% survival in most centers.[72,76,138,143] When infant surgery became possible, success with atrial baffle procedures progressed even further and many of the preoperative problems associated with hypoxemia and polycythemia were reduced by early repair.[26,77,139,144] Today, in most centers, a survival rate of over 95% would be expected for atrial baffle repair of transposition during infancy, usually by the Senning operation.[145,146] In the late 1960s, many centers did not routinely perform cardiac catheterization on patients who had survived the Mustard operation, especially when they were clinically doing well. A few patients were noted to have clinically significant venous obstruction but most were felt to have an excellent result with no residual hemodynamic abnormalities. In the early 1970s, baffle obstruction was more frequently recognized as routine postoperative cardiac catheterizations were performed. It became apparent that about 10 to 20% of patients who underwent the Mustard operation had significant systemic venous obstruction postoperatively.[30,147–149] While some were severe enough to require reoperation, others were either not clinically apparent or the findings

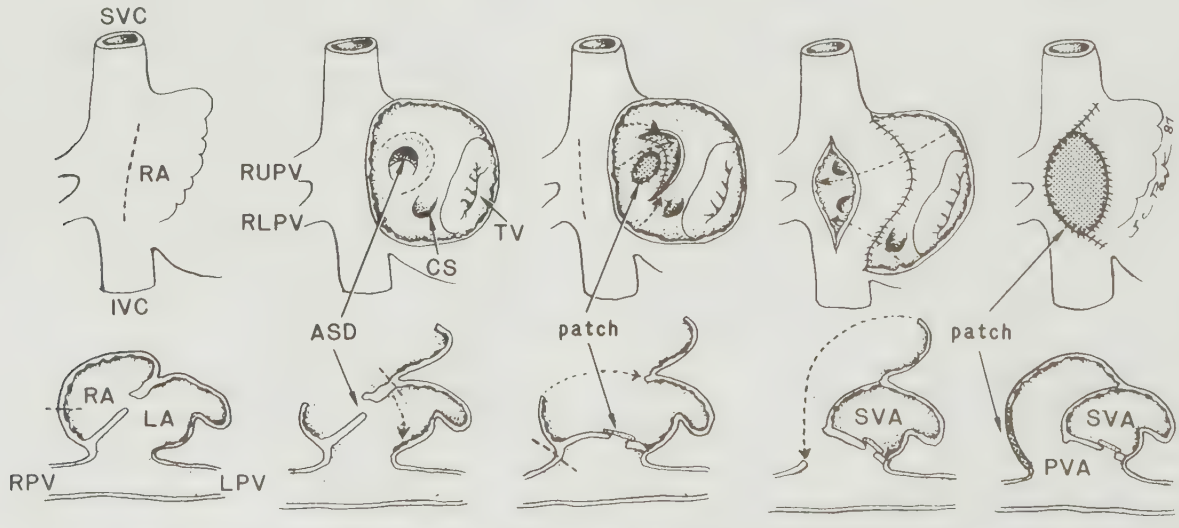

Fig. 71–28. Diagram illustrating the Senning operation (see text). Top: surgical view of the repair through the right atrium. Bottom: cross-section view of each sequence of the repair. See Fig. 71–27 for legend to abbreviations.

were subtle and often overlooked.[30,148] Pulmonary venous obstruction has been found less frequently, in about 5 to 10% of survivors, often occurring as a late complication.[148–151] These were commonly more severe degrees of obstruction that required reoperation. It was initially thought that these problems with venous obstruction were related to shrinkage of the pericardium used for the atrial baffle.[152] This led to the use of a variety of synthetic materials including Dacron and Gore-Tex as well as a variety of different shapes being recommended for the baffle to avoid these problems. As additional experience was gained with each of these methods and types of materials, it became obvious that most of the problems were related to the size and placement of the baffle rather than the material that was used. In the form in which the Mustard procedure finally evolved, most surgeons preferred to put in a large enough baffle to ensure an adequate opening across the superior and inferior vena caval inlet and enlarged the lateral wall of the right atrium with a patch to prevent obstruction in the new pulmonary venous atrium.

Atrial arrhythmias are another important problem in patients who have undergone a Mustard operation. It was common for patients to have sinus arrest with a junctional escape rhythm and episodes of supraventricular tachycardia in the early postoperative period. These abnormal findings usually resolved and these patients initially were then thought to be in sinus rhythm. In the early 1970s reports began to appear of atrial arrhythmias and sick sinus syndrome in patients who had undergone Mustard repair.[78,91] It was suggested by El-Said et al.[91] that these patients were not truly in sinus rhythm, and it quickly became apparent from this and other studies that direct damage to the sinus node and/or to the sinus node artery frequently occurred at the time of Mustard operation.[18,91] Longterm followup studies from our institution[80] and others[91–96] indicated that the percentage of atrial arrhythmias continued to increase in frequency with increasing length of postoperative followup. On the basis of these investigations, surgeons modified the operative technique to avoid cannulation in the area of the sinoatrial node and judiciously placed sutures in the high right atrial portion of the baffle to avoid injury to the sinus node artery along its expected course.[153] Particular attention was also paid to placement of sutures in the region between the coronary sinus and tricuspid valve to avoid damage to the atrioventricular node.

Lastly, the surgical technique was altered to avoid incision in the roof of the coronary sinus.[143,144] In the standard Mustard technique, the roof of the coronary sinus was incised back toward the left atrium for the purpose of including the unoxygenated coronary sinus drainage on the systemic venous side of the baffle. It was theorized that the removal of the atrial septum had destroyed the anterior and middle internodal pathways while the "unroofing" of the coronary sinus destroyed the remaining posterior internodal tract thereby producing the atrial arrhythmias seen postoperatively. Although there has been some discussion as to whether or not these internodal tracts exist either physiologically or anatomically, the decision was made for both the Mustard, and later the Senning operations, to leave the coronary sinus untouched and allow it to drain on the pulmonary venous side of the baffle. This results in slight systemic desaturation; however, this appears to be of little consequence. Unfortunately, all of these modifications mentioned above occurred over a short time period and it is impossible to determine whether this latter modification had any direct beneficial effect or was just temporally related to the benefits that resulted from the techniques that were designed to avoid injury to the sinoatrial node.

In the period around 1980, it seemed obvious that these modifications of the Mustard procedure had been successful. Junctional rhythm and supraventricular tachycardia were uncommon in the early postoperative period and pulmonary or systemic venous obstruction were much less commonly seen both in the early postoperative period and on late followup. Although there was not uniform agreement as to which material should be used for the atrial baffle, equally good results were obtained with either pericardium or synthetic materials. At about this time reports of success with the Senning operation began to appear.[118,154] Since this operation used the patient's native atrial tissue rather than nonviable material for the atrial baffle, its proponents suggested that the use of this technique would eliminate most of the postoperative problems that were found following the Mustard operation. On this basis, the Senning operation became the atrial baffle procedure of choice, in most centers, for the repair of transposition.[145,146,155–157] Initial results with this procedure were encouraging but it is difficult to determine whether the improvements in postoperative complications were as a result of factors inherent in the Senning procedure, or were as a result of experience that was gained in attempts to avoid these complications from the Mustard operation. In our own series of 45 patients who have had a Senning operation, systemic venous obstruction is uncommon. However, pulmonary venous obstruction occurs with a similar frequency as was found following the Mustard procedure. This is true even though a patch has been placed in the lateral wall of the right atrium to enlarge the new pulmonary venous atrium in an attempt to avoid the problem of pulmonary venous obstruction. In addition, junctional rhythm was present intraoperatively or in the early postoperative period in over 60% of our series. Although almost all patients were in sinus rhythm by the time of discharge, a few have had problems with atrial flutter, 30% have prolonged sinus node recovery time on postoperative cardiac catheterization and junctional rhythm is present in two of the earliest patients in the series who are now 7 years postoperative. Similar findings have also been reported by others.[158,159] It should be emphasized that problems with venous obstruction, atrial arrhythmias, and sinus node dysfunction were not reported until 5 or 6 years after the beginning of the Mustard operation era. This is particularly true of the electrophysiologic abnormalities since many patients exhibited these problems only on late followup. Thus, although the Senning operation is easier to perform on the small infant and at this point appears to have a lower frequency of complications as compared to the Mustard operation, only longterm followup over the next decade will provide conclusive proof that it is the superior of the two atrial baffle procedures.

Tricuspid valve incompetence has been reported to occur following atrial baffle operations. It is possible that this is caused by the inability of the tricuspid valve to function as the systemic atrioventricular valve over a long period of time in some cases. However, in the majority of patients, tricuspid incompetence is found early postoperatively and is probably in some way related to the operative procedures. Tynan et al.[160] suggested that this abnormality was related to arrhythmias developing as a result of surgery. However, in our series,[30] and in others,[79,148,149] tricuspid incompetence was most often seen in patients who had closure of

a ventricular septal defect through the tricuspid valve. This suggests injury to the valve structure or its support apparatus at the time of operation. Fortunately, postoperative tricuspid valve incompetence occurs in less than 5% of patients and is usually mild.[141] However, since this valve must tolerate systemic pressure for many years, even a mild degree of incompetence may become a significant and potentialy lethal complication over the long term.

Another major problem that is yet unsolved is the concern about the ability of the right ventricle to function as the systemic ventricle over a patient's lifetime. Many investigators have studied systemic right ventricular function in patients following the Mustard operation and these studies conclude that ventricular function is generally below normal despite the fact that these patients seem to be well and appear to be able to function normally.[161–164] However, some of these conclusions may be misleading. The normal values used to assess function of a systemic left ventricle may not be directly applicable to the systemic right ventricle. In addition, many patients who clearly have systemic ventricular dysfunction as compared to their postoperative peers with transposition had this abnormality preoperatively, or on the basis of problems encountered during the perioperative period. This is supported by Graham et al.[165] who found improved right ventricular function in a group of patients who underwent a Senning procedure as compared to a group of patients who had a Mustard operation. This improved right ventricular performance may be due to a younger age at operation, better preoperative myocardial function, or improved intraoperative myocardial protection.[165] It appears that patients who have good postoperative systemic ventricular function generally maintain this good function over a long period of time. Since many of the patients who were the first to undergo atrial baffle repair are currently only entering their third postoperative decade, the question of the ability of the right ventricle to function as the systemic ventricle for a patient's lifetime remains to be answered.

Arterial Switch Repair

The concerns about longterm systemic ventricular function, along with problems of baffle obstruction and electrophysiologic abnormalities that are present with both types of atrial baffle repair, led surgeons to reconsider the possibility of an arterial switch repair. It has always been technically relatively easy to divide the transposed great arteries and reanastomose the vessels so as to provide a concordant ventriculoarterial connection. The problem, of course, lies in the fact that the coronary arteries arise from the sinuses of the semilunar valve that is connected to the right ventricle. Since this becomes the pulmonary valve after an arterial switch repair, the coronary arteries would be perfused with low pressure, unoxygenated systemic venous blood and this is invariably fatal. In the past, a wide variety of procedures for reconnecting one or both coronary arteries to the aorta were suggested or attempted. These procedures were all unsuccessful until the report by Jatene in 1975[81] of survival following an arterial switch repair that included transplantation of both coronary arteries into the reconnected aorta. This technique included the removal of the coronary arteries from the base of the aorta by excision of a cuff of aorta about the coronary orifice and anastomosis of this cuff to two similar size openings made in the base of the pulmonary artery where it arises from the left ventricle (Fig. 71–29A and B). The aorta is then reconnected to the proximal stump of the pulmonary artery while the pulmonary artery is connected to the proximal stump of the aorta (Fig. 71–29C).

The arterial switch repair initially was met with great enthusiasm but, unfortunately, the initial experience with this procedure in most centers was discouraging. The mortality was generally over 70%[166] and most centers returned to using an atrial baffle procedure for repair of transposition. However, a few centers continued to perform arterial switch repair and reported a dramatic increase in survival as more procedures were performed.[141,166,167] This convinced some additional centers to again attempt to perform the arterial switch operation. It has become apparent that there is a "learning curve" for the surgical team that performs this operation.[166,168] As more centers begin to perform the arterial switch repair, the mortality due to this "learning curve" can be minimized by consultation and close collaboration with those centers that have already been successful in avoiding the problems and pitfalls that are associated with this initial high mortality.

The ability of the left ventricle to function against systemic pressure and resistance is an essential factor for a successful arterial switch repair. In the patient with transposition of the great arteries and an intact interventricular septum, the left ventricular pressure usually falls to below half systemic level within the first week of life and loses this ability to function against systemic pressure by about the third week of age. In the patient with left ventricular outflow tract obstruction, systemic pressure may be present in the left ventricle after the first month of life. However, an arterial switch repair cannot be performed since this will result in obstruction to outflow in the systemic ventricle postoperatively. In transposition with a large patent ductus arteriosus or with a ventricular septal defect, pulmonary hypertension may persist, and the left ventricle will thus retain its ability to function as the systemic ventricle. In these patients, in contrast to the patient with an intact interventricular septum and low left ventricular pressure, the arterial switch repair can be delayed until a few months of age.[167,169] However, early operation may be required because of congestive heart failure or concerns about pulmonary vascular disease. If early repair is not possible and banding of the pulmonary artery is performed in the patient with a ventricular septal defect, congestive heart failure and concerns about pulmonary hypertension can be reduced or eliminated while left ventricular pressure remains at systemic level.[167] An arterial switch repair can then be performed later during infancy, or even during childhood, when it may be easier to attempt to close the ventricular septal defect. As was previously discussed in the section on palliative procedures, pulmonary artery banding also has been used in some centers to "prepare" the left ventricle in transposition of the great arteries with an intact interventricular septum, when the patient is beyond the neonatal period.[141]

There are a number of areas of concern in patients who have survived an arterial switch repair. The maintenance of normal coronary artery blood flow is of major importance. In general, it is likely that those patients with compromise of the coronary circulation do not survive operation. However, we have had occasion to perform a heart transplant on an 18-month-old patient who underwent an arterial switch at another institution and sustained a severe myocardial infarction. In some instances, myocardial ischemia may result from kinking of the coronary artery or external compression by the surrounding tissue or the newly connected pulmonary artery.[167] If these problems are recognized in the early

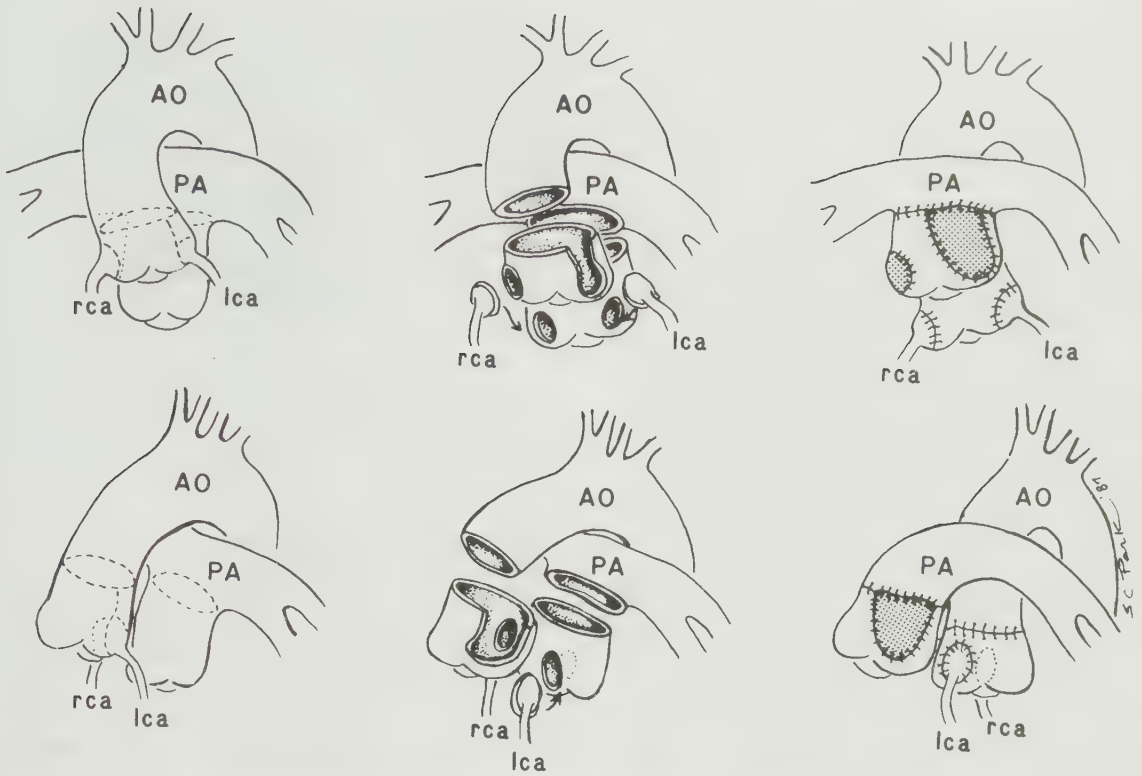

Fig. 71–29. Diagram illustrating the arterial switch repair (see text). Top: frontal view. Bottom: sagittal view. Ao = aorta, PA = pulmonary artery, lca = left coronary artery, rca = right coronary artery.

postoperative period then reoperation might be attempted. Another concern is the site of the anastomosis for reconnection of the great arteries. The reported difficulties usually have been with pulmonary artery stenosis and some patients have required reoperation to correct this problem.[166,167] At the time of primary repair, a patch of synthetic material is generally used to enlarge the pulmonary artery at the site of anastomosis. In addition, patches are also placed over the openings that result from the removal of the coronary arteries with the surrounding cuff of what was formerly the wall of the aorta. Some cases of stenosis at the site of the aortic anastomosis have also been reported but these are generally mild and have rarely required reoperation.

The long-term results of patients who have undergone an arterial switch repair for transposition of the great arteries are still unknown. Even though these above problems may not be present postoperatively in an infant who has undergone arterial switch repair in the first few weeks of life, there is still concern about growth of the anastomotic sites, or about possible compromise of transplanted coronary arteries as the patient grows to adulthood. It is only with time and additional experience that the question of whether an atrial baffle procedure or the arterial switch repair is preferable for the surgical management of the patient with transposition of the great arteries.

Rastelli Operation

The various procedures that have been described in this chapter have rarely been used successfully in the management of the patient with transposition of the great arteries, a ventricular septal defect and severe subpulmonic stenosis (complex transposition) (Fig. 71–30A). Although it is possible to close the ventricular septal defect in these patients, it is usually not possible adequately to relieve the muscular subpulmonic left ventricular outflow tract obstruction. As a result, most patients died and the few that did survive still had residual severe left ventricular outflow obstruction. In 1969 Rastelli et al.[113] described a procedure to repair complex transposition in which no attempt is made to resect the subpulmonic left ventricular outflow obstruction. An incision is made in the right ventricle and a patch is placed between the inferior border of the ventricular septal defect and to the right side of the outflow to the aorta (Fig. 71–30B). The pulmonary artery is oversewn and thus the outflow of the left ventricle is directed through the ventricular septal defect and out into the aorta. If it is felt that the ventricular septal defect will be inadequate to handle the systemic blood flow without obstruction, then the defect is enlarged prior to placement of the patch.[170] After the defect has been closed, one end of a conduit is connected to the incision in the right ventricle and its distal end is anastomosed to the pulmonary artery (Fig. 71–30C). The result of this operation is that the oxygenated, left ventricular blood is expelled into the aorta while the unoxygenated systemic venous return is ejected from the right ventricle through the conduit and into the pulmonary artery.

In general, a valved conduit has been used in the Rastelli procedure. Initially, a homograft aorta with its aortic valve and the anterior leaflet of the mitral valve still attached, was used. Most centers in England continue to use the homograft aorta with considerable success.[171,172] In the United States, problems of homograft calcification[173] and homograft availability led to the use of

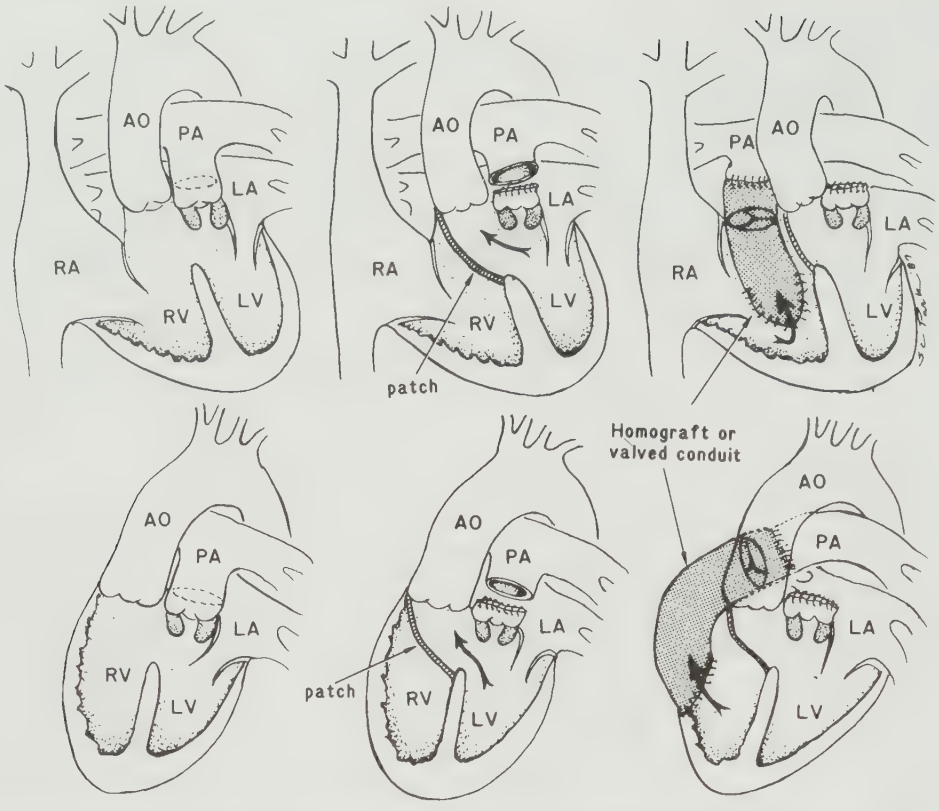

Fig. 71–30. Diagram illustrating the Rastelli operation (see text). Top: frontal view. Bottom: sagittal view. Ao = aorta, PA = pulmonary artery, LA = left atrium, RA = right atrium, LV = left ventricle, RV = right ventricle.

conduits of synthetic material that contained a porcine heterograft aortic valve. These conduits were used successfully and resulted in a better than 75% survival rate for the repair of patients with complex transposition.[170,174,175] Unfortunately, these heterograft conduits did not withstand the test of time and stenosis often occurred either due to an extensive, thickened endothelial lining and/or severe fibrosis and calcification of the heterograft porcine valve.[176] In most cases with significant obstruction it was necessary to remove the heterograft valve conduit and this was usually replaced successfully with a nonvalved conduit also of synthetic material.[174,177] In recent years, many centers have begun successfully to use a conduit of homograft pulmonary artery containing the pulmonary valve. These are freeze-dried and are available commercially in a wide variety of sizes. The longterm fate of these conduits is still unknown.

Other problems that have occurred following a Rastelli procedure for complex transposition include residual ventricular septal defects and pulmonary artery stenosis. An unrecognized defect, especially in the apical region of the muscular septum may be found postoperatively. However, this has become much less common as a result of preoperative evaluation with two-dimensional and Doppler echocardiography and careful high-quality angiocardiography in axial projections. Fortunately, when an anatomic defect is not a result of incomplete surgical closure and is newly recognized postoperatively, it is generally small and is of little clinical importance. On the other hand, it is important to assess the physiologic consequences of any residual ventricular septal defect of significant size. If there is more than twice normal pulmonary blood flow as a result of the defect, especially if the pulmonary artery pressure is also elevated, then the patient might be at risk for the development of pulmonary vascular disease and reoperation for closure of the defect would have to be considered. Abnormal postoperative ventricular function would be another indication for considering closure of a residual defect with a moderate shunt, even in the absence of pulmonary hypertension, since the increased volume load might further stress or compromise the ventricle.

Right ventricular hypertension may be caused by pulmonary artery stenosis.[178] This problem is more commonly found postoperatively in the patient with complex transposition when severe pulmonary stenosis or pulmonary atresia with resultant hypoplasia of the pulmonary artery tree is present preoperatively. If stenosis is found proximally, either at the right ventricular side of the conduit anastomosis, in the conduit itself, or at a proximal site of pulmonary artery anastomosis, then reoperation might successfully relieve the gradient. Unfortunately, it is often the case that the areas of stenosis are at a distal anastomosis between the conduit and small pulmonary arteries and these are usually not amenable to re-operation. In patients with tetralogy of Fallot, it has been suggested that preoperative measurement of the size of the pulmonary arteries angiographically is predictive of the postoperative right ventricular pressure and may be valuable in selecting patients for operation.[179] This formula may also be useful in patients with complex transposition and pulmonary artery stenosis. This technique is discussed in greater detail in the section on surgical management in Chapter 63 on tetralogy of Fallot.

Lastly, patients who have undergone repair of complex transposition with a Rastelli procedure may be at similar risk for the

development of postoperative atrioventricular conduction abnormalities and ventricular arrhythmias as are patients who have undergone repair of tetralogy of Fallot.[180,181] In both procedures, a right ventriculotomy is performed and there is patch closure of the ventricular septal defect. Although removal of infundibular muscle in the right ventricular outflow tract is only performed in repair of tetralogy, patients seem to be at similar risk from both procedures for the development of arrhythmias postoperatively. Thus, patients who have undergone Rastelli repair for complex transposition should have careful postoperative followup including hemodynamic and angiographic assessment, 24-hour ambulatory monitoring and stress exercise testing. It has been suggested that ventricular arrhythmias in the presence of right ventricular hypertension following repair of tetralogy of Fallot puts the patient at greater risk for sudden death. It is likely that patients who have undergone a Rastelli procedure are at similar risk in the presence of the same circumstances, however, this has not been firmly established.

SPECULATION ABOUT THE FUTURE

As we approach the twenty-fifth anniversary of the Mustard repair and of balloon septostomy, the management of the infant with transposition of the great arteries still varies greatly from center to center. The longterm outlook and longevity of patients who have undergone atrial baffle repair is still in doubt as a result of problems with arrhythmias and the question of the ability of the right ventricle to function as the systemic ventricle for an entire lifetime. The arterial switch repair seems to be an attractive alternative with the hope of eliminating these problems and concerns of repair using atrial baffle techniques. On the other hand, longterm followup is yet unavailable in these patients and problems with arterial anastomoses or the reimplanted coronary arteries are potential areas of future concern. The initially high surgical mortality has been reduced in those centers continuing to perform arterial switch repairs. However, the survival rate for this procedure is approaching but still does not match that of atrial baffle repair. In view of the potential great longterm benefits, the question arises should all centers now be performing the arterial switch repair? On the other hand, since there is a high mortality with the initial series of procedures in any given center, should the arterial switch be done in only a select number of centers? Although all of these questions remain to be answered, the last 25 years have brought life and hope to countless numbers of patients with a previously fatal abnormality. Hopefully, this progress will continue to take place over the next 25 years as well.

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CHAPTER 72

Double-Outlet Ventricles

Michael J Silka

The concept of the double-outlet ventricle refers to a specific type of ventriculoarterial connection, in which both great arteries arise primarily from one ventricle.[1] The diagnosis of double-outlet right ventricle (DORV) applies when all of one and more than 50% of the other great artery arise from the morphologic right ventricle.[2,3] By similar convention, double-outlet left ventricle (DOLV) is diagnosed when both great arteries arise entirely, or predominantly, above the morphologic left ventricle.[4,5] Although the preceding definitions are conceptually simple, abnormal ventriculoarterial (VA) alignments remain difficult to characterize and categorize precisely, and continue to be the source of considerable controversy.[6] The concept of the double-outlet right or left ventricle refers only to a specific ventriculoarterial connection; considerable variations due to associated cardiac malformations and segmental connections must be considered separately. These anomalies, however, can be grouped in such a way as to provide significant physiologic and surgical information.[7] As DORV has a clearly established anatomic and embryologic basis, and is of much greater frequency than DOLV, it will be the primary emphasis of this chapter.[8,9]

DORV refers to a diverse group of congenital heart defects, with the common feature of origin of both great arteries primarily from the morphologic right ventricle. Identification of this type of ventriculoarterial connection does not specify the associated physiology, which may simulate that of a large ventricular septal defect, tetralogy of Fallot, or transposition of the great arteries. DORV is a rare defect, representing approximately 1.5% of recognized congenital heart disease.[10]

Because of the anatomic subsets of this defect, and association with other congenital heart defects, marked differences in medical and surgical prognosis exist within this group.[11] Recent advances in echocardiography and cardiac catheterization have clarified the variable pathology of this lesion, and provide the basis for the current definition of DORV.

Historically, a number of terms have been used for this malformation, including the Taussig–Bing complex,[12] partial transposition,[13] origin of both great vessels from the right ventricle,[9] and double-outlet right ventricle.[13] The initial definitions of DORV required that both great arteries arise completely from the right ventricle, with no fibrous mitral-semilunar continuity. Improved understanding of surgical and pathologic anatomy has resulted in the recognition that DORV represents a continuum of congenital heart defects, extending from ventricular septal defect with marked aortic override, followed by classic origin of both great vessels from the right ventricle, proceeding next to the Taussig–Bing complex, and finally transposition of the great arteries with pulmonary override of the ventricular septal defect. Thus, we define DORV in accordance with the classic study of Lev and colleagues: "Double-outlet right ventricle is an anomaly in which two cusps and part of the third of both semilunar valves arise from the right ventricle."[2] We recognize that other criteria for DORV have been offered; however, a diagnosis predicated on a specified amount of mitral-semilunar discontinuity or the requirement of absolute arterial override is inconsistent with the recognized spectrum of ventriculoarterial connections.[14] A descriptive, segmental approach,[15] of which double-outlet right ventricle is one component, will provide accurate anatomic and clinical definition.

ANATOMIC CONSIDERATIONS

As DORV refers to a specific type of ventriculoarterial connection, further classification is required, based on the presence and type of associated congenital heart defects and segmental connections. For this chapter, DORV will be restricted to anatomy in which there are two ventricles, and in which a ventricular septal defect is usually present and provides the only outlet for the left ventricle. The anatomic description of DORV requires three basic considerations: 1) the relationship of the great arteries; 2) the morphology of the ventricles and their outflow tracts; and 3) the presence of associated congenital cardiac defects. To describe these features, we will use the anatomic nomenclature proposed by Anderson et al.,[16] while recognizing that this terminology is not universal.

Any muscular structure that separates a semilunar valve from an atrioventricular valve will be defined as the ventriculoinfundibular fold. In the usual setting of DORV, this is the structure responsible for mitral-semilunar disontinuity. The size of this structure is variable, and determines the distance between the ventricular septal defect and the semilunar valve. This structure has also been termed the second parietal band[17] (Fig. 72–1).

The trabecula septomarginalis refers to the extensive septal trabeculation of the right ventricle. Superiorly, the trabecula septomarginalis divides to form two limbs, with the outlet septum fusing with the muscular septum at this bifurcation in the normal right ventricle. In most forms of DORV, however, the ventricular septal defect is cradled between these two limbs of the trabecula septomarginalis, and there is associated deviation of the outlet septum. This is the predicted location of the ventricular septal defect in DORV whether the ventricular septal defect is subaortic, subpulmonic, or doubly committed. The variable relation of the ventricular septal defect to the great arteries depends on the plane and extent of the outlet septum, and the relation of the great arteries.

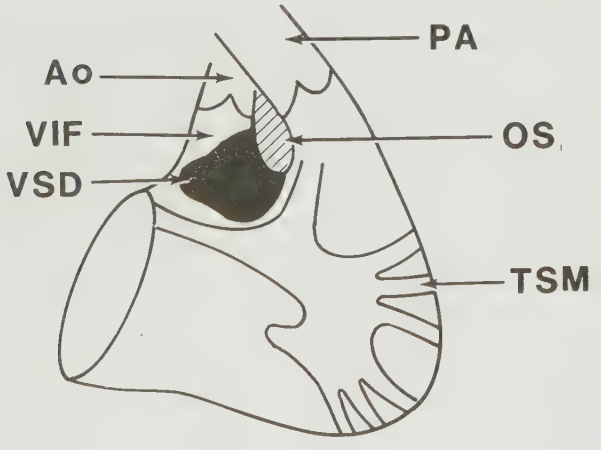

Fig. 72–1. Morphologic aspects of the double-outlet right ventricle with normally related great arteries. The right ventricle is illustrated as if the anterior free wall has been removed. The following structures are emphasized: 1) The ventriculoinfundibular fold (VIF), separating the atrioventricular and semilunar valves; 2) the trabeculaseptomarginalis (TSM) with the ventricular septal defect (VSD) cradled between the two limbs; and 3) the outlet septum (OS), separating the aorta (Ao) and pulmonary artery (PA).

Thus, the location of the ventricular septal defect in DORV is not random. The exception to this rule of location is the noncommitted ventricular septal defect, in which the defect is either apical trabecular, or membranous with inlet extension.[18]

The outlet (or infundibular) septum refers to the muscular division between the subaortic and subpulmonic outflow tracts. Also referred to as the conal septum or first parietal band,[17] the orientation and extension of this structure relative to the ventricular septal defect is variable. In DORV, the long axis of the outlet septum is directed toward the right ventricle, deviated from the plane of the muscular septum.

Using this terminology, DORV may be categorized into major subgroups based on the relation of the great arteries and consideration of location of the ventricular septal defect, with subsequent consideration of the presence or absence of associated cardiac anomalies.

Relations of the Great Arteries in Double-Outlet Right Ventricle

Three basic relations of the great arteries in association with DORV are recognized. The most frequent is a normal relation, with the aortic annulus posterior and to the right of the pulmonary annulus, with a subsequent spiral course of the great arteries. The second common relation is the aorta to the right of the pulmonary trunk, with a subsequent parallel course (side by side) of the great arteries. A third, and much less frequent form of DORV connection occurs with the aorta anterior and to the left of the pulmonary trunk (Fig. 72–2). Piccoli et al. have proposed classifying the forms of DORV according to the relation of the great arteries which is predictive of the anatomy of the associated ventricular septal defect.[19] This is of paramount importance, as the relation of the ventricular septal defect to the aorta will largely determine surgical alternatives.

Double-Outlet Right Ventricle with Normally Related Great Arteries

In this subtype of DORV, the aorta is posterior and to the right of the pulmonary artery. This resembles the arterial relation seen in the normal heart or in tetralogy of Fallot. Almost without exception, the finding of relatively normally related great vessels in DORV defines the ventricular septal defect as related to the sub-

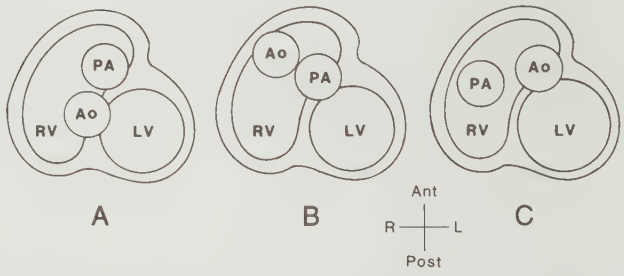

Fig. 72–2. Short axial view of the types of semilunar valve relations in double-outlet right ventricle. The aorta annulus (Ao) may be related to the ventricular septal defect either when posterior and right, or anterior and left (A and C). However, an anterior and rightward position of the aorta (B) is associated with a subpulmonic position of the ventricular septal defect.

aortic outflow tract. The proximity of the aortic valve to the ventricular septal defect will be determined by the dimensions of the ventriculoinfundibular fold. The associated absence or presence of pulmonic and subpulmonic stenosis will determine the magnitude of pulmonary blood flow and clinical presentation (Fig. 72–1). Rarely, the ventricular septal defect will be doubly committed or noncommitted.

The differentiation of DORV from tetralogy of Fallot is controversial in this setting.[2,20] Edwards has emphasized that DORV defines a type of ventriculoarterial connection, while tetralogy of Fallot refers to a specific infundibular septal malalignment.[6] The two terms are distinct, but not mutually exclusive. Tetralogy of Fallot with extreme aortic override represents one point in the spectrum of the diverse congenital heart defects grouped as DORV (Fig. 72–3).

Double-Outlet Right Ventricle with Parallel Great Arteries and Aorta to the Right

A significant difference in the alignment of the semilunar valves is anticipated when the great arteries are of a more or less parallel course, with a rightward and anterior origin of the aorta. In the continuum of DORV, this arterial relation will identify the left-sided pulmonary trunk as adjacent to the ventricular septal defect, within the limbs of the trabecula septomarginalis. The fusion of a well-formed outlet septum with the posterior limb of the ventriculoinfundibular fold confines the defect to a subpulmonary position (Fig. 72–4). This is in contrast with the subaortic defect, in which the infundibular septum inserts into the superior (anterior) limb of the trabecula septomarginalis. In either arterial relation, hypoplasia of the outlet septum results in a doubly committed ventricular septal defect.

The Taussig–Bing malformation is properly considered within the context of side-by-side great artery relations with an associated juxtapulmonary (supracristal) ventricular septal defect. Exact definition of the original heart described by Taussig and Bing is controversial, depending on consideration of the commitment of the pulmonary artery to the right or left ventricle.[21,22] The presence of a bilateral infundibulum is considered by some to be requisite to the strict definition of the Taussig–Bing heart,[23] while others dispute the significance.[2,3]

With further dextrorotation of the aorta, the ventricular septal defect remains closely related to the posterior pulmonary trunk. However, the defect now is subcristal in location, not as superior as noted in the classic Taussig–Bing malformation. It has been proposed that all cases of juxtapulmonary ventricular septal defect with malalignment of the infundibular septum be classified as the "Taussig–Bing" malformation due to common morphologic features that determine the surgical options.[24] DORV with d-transposition may more adequately describe the anatomy and physiology of this lesion.

Double-Outlet Right Ventricle with Aorta Anterior and Left

A much less frequent type of DORV connection is an anterior and leftward origin of the aorta with a subsequent parallel course of the great arteries. The aortic position approximates that identified in "corrected" transposition. Although this great artery re-

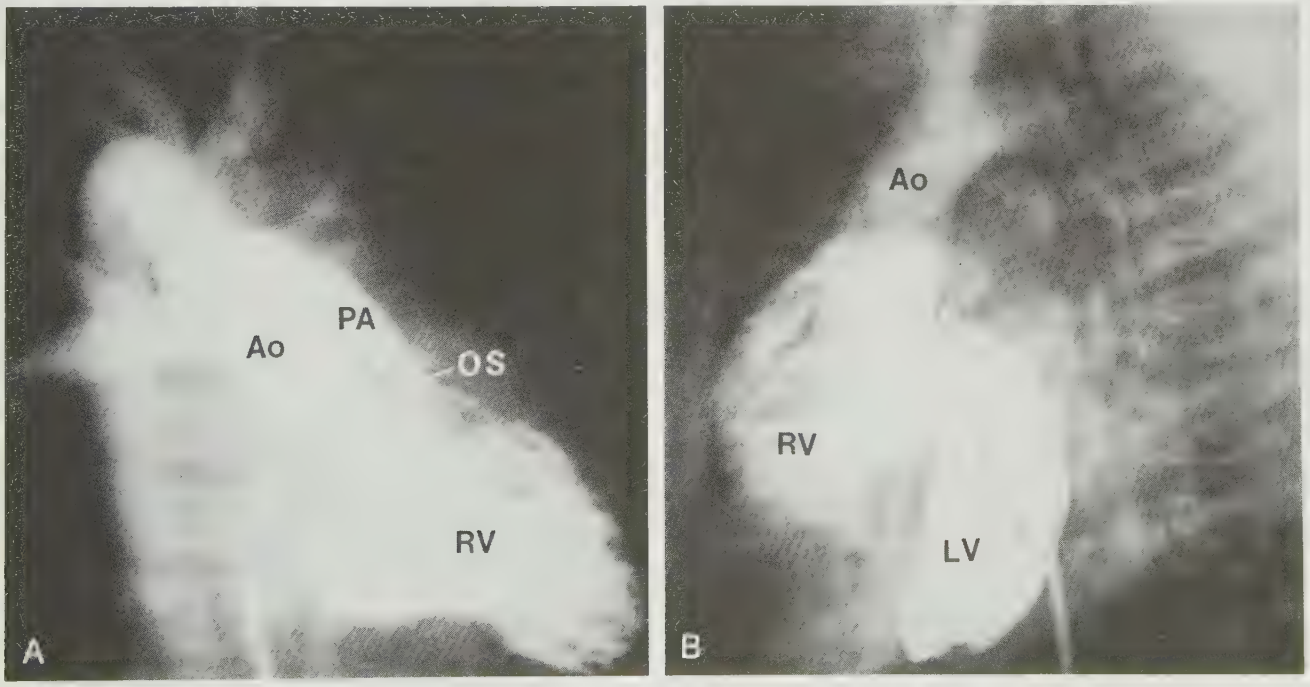

Fig. 72–3. Double-outlet right ventricle with normally related great vessels and severe subvalvar and valvar pulmonic stenosis. A) Frontal view right ventricular (RV) angiogram demonstrating severe anterior displacement of the outlet septum (OS), and a right aortic arch. B) Left ventriculogram (LV) in the left anterior oblique projection. The LV is relatively hypoplastic, and the aorta (Ao) is committed to the anterior RV, in distinction to overriding the VSD as in classic tetralogy of Fallot.

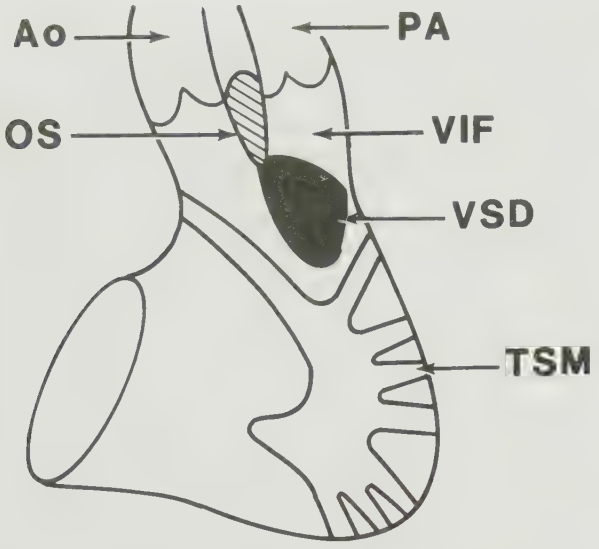

Fig. 72–4. Double-outlet right ventricle with side-by-side great arteries and subpulmonic ventricular septal defect. The outlet septum (OS) is related to the posterior (inferior) limb of the trabecula septomarginalis (TSM), with the ventricular septal defect related to the posterior pulmonary annulus. Attenuation of the ventriculoinfundibular fold (VIF) results in a juxtapulmonary ventricular septal defect, initially described as the Taussig–Bing anomaly.

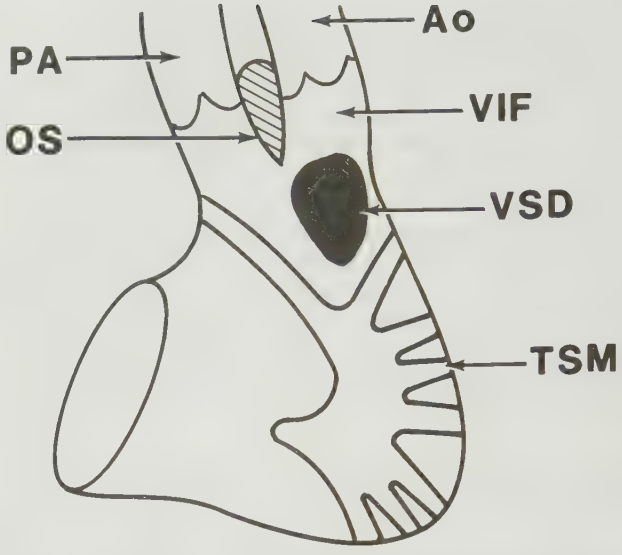

Fig. 72–5. An anterior and leftward position of the aortic annulus is associated with insertion of the outlet septum posterior to the superior limb of the trabecula septomarginalis (TSM). This position of the ventricular septal defect is similar to that when the great arteries are side by side and the ventricular septal defect is subpulmonic. However, differing degrees of rotation and extension of the outlet septum result in significant variability in the outflow anatomy of this defect.

lation is most frequently associated with a subaortic ventricular septal defect, the somewhat variable aortic position in this setting may result in a significant alteration in the morphology of the ventricular septal defect. The infundibular septum inserts posterior to the superior limb of the trabecula septomarginalis, so that the ventricular septal defect resembles that seen in the subpulmonary position when the aorta is right sided (Fig. 72–5). When the defect is doubly committed, both great arteries may override the ventricular septal defect. Brandt et al., have termed this "double-outlet both ventricles,"[25] extending the continuum of the double-outlet ventricles toward a double-outlet left ventricle.

The Ventricular Septal Defect in Double-Outlet Right Ventricle

The relation of the great arteries defines, in part, the location of the ventricular septal defect in DORV, based on the insertion of the outlet septum. The inferior margins of the ventricular septal defect are the two limbs of the trabecula septomarginalis, except in the noncommitted ventricular septal defect. In spite of these constants, variability in the size of the ventricular septal defect will occur due to the morphology of the ventriculoinfundibular fold and the degree of extension of the infundibular septum. Four types of interventricular communications are identified in DORV:

1. Subaortic ventricular septal defect: This is the defect location in the setting of normally related great vessels, and most frequently when the aorta is anterior and leftward. The ventriculoinfundibular fold is interposed between the ventricular septal defect and the aortic valve, resulting in a muscular border around the entire defect. Attenuation of the ventriculoinfundibular fold would result in a perimembranous ventricular septal defect, with aortic override, while associated cephalad deviation of the infundibular septum would result in tetralogy of Fallot. The various forms of pulmonary stenosis are frequently associated with DORV and subaortic ventricular septal defect due to deviation of the infundibular septum.
2. Subpulmonic ventricular septal defect: This is the defect location when the aorta annulus is to the right and/or anterior to the pulmonary annulus. This defect may be either muscular or perimembranous, predicated on the extent of the ventriculoinfundibular fold. Left-sided obstructive cardiac lesions most frequently occur in association with this anatomy.[26]
3. Doubly committed defects: Absence or marked hypoplasia of the infundibular septum will result in override of the ventricular septal defect by both great arteries. When totally absent, both great arteries may override the ventricular septum.
4. Noncommitted defects: An apical trabecular or membranous-inlet ventricular septal defect is remote from both great arteries in DORV, and thus termed noncommitted. Atrioventricular septal defects are the most frequent type of VSD associated with this type of DORV.[27]

Varying degrees of left ventricular outflow obstruction may result from a restrictive ventricular septal defect or an intact ventricular septum. As the ventricular septal defect provides the outflow tract for the left ventricle in DORV, it has been termed "physiologically advantageous."[28] The actual incidence of a restrictive ventricular septal defect in DORV (i.e., systolic pressure gradient between the left and right ventricle) has been reported to be 3%.[29,30] However, more recent studies using two-dimensional echocardiography have indicated that a small ventricular septal

defect, requiring enlargement at the time of surgery, may be much more common than initially reported.[31] Recognition of a restrictive defect is mandatory before surgical repair is attempted, as the interventricular communication can be safely enlarged superiorly[32] (Fig. 72–6).

Isolated cases of spontaneous closure of the ventricular septal defect in the setting of DORV have been reported. Most frequently they have been associated with hypoplasia of the mitral valve apparatus or left ventricle,[33] although instances of ventricular septal defect closure with previously normal left ventricular anatomy have been reported.[34,35] Survival is based on left-to-right atrial shunting in this setting.

EMBRYOLOGY

Double-outlet right ventricle represents a relatively primitive embryologic defect within the group of bulboventricular malformations. At Streeter horizon 15, the primitive truncus completely overrides the primitive right ventricle, with the future aortic valve to the right of the future pulmonic valve. At this stage of embryogenesis, three events appear necessary to result in the production of normal ventricular outflow tracts: 1) clockwise inversion of the distal conus, which results in a posterior location of the future aortic valve; 2) leftward shift of the conoventricular junction, committing the aortic conus to the left ventricle; and 3) subsequent differential absorption of the subaortic conus resulting in mitral-aortic continuity.[36] Goor and Edwards[37] have proposed that DORV be included within the "spectrum of transposition complexes," based on a common failure of conal inversion. Failure of leftward shift of the primitive conus would result in persistence of origin of both great vessels from the right ventricle, while subsequent differential conal absorption in the absence of "inversion" would result in transposition of the great arteries. Anderson et al. expanded these concepts to a spectrum of bulboventricular malformations extending from tetralogy of Fallot to transposition of the great arteries, with DORV representing the intermediate expression of basic defects of conal absorption and rotation. Emphasis was also placed on the orientation of the anterior muscular septum in defining the relationship of the great arteries of the ventricular septal defect.[38] The intermediate morphologic forms of DORV with transposition or DORV with tetralogy of Fallot are determined by the orientation of the conal septum and relative extent of conal rotation.

A variable degree of conal absorption accompanies failure of conoventricular shift and absence of distal inversion in DORV. In the setting of primary persistence of the subpulmonic conus, the ventricular septal defect tends to be subaortic, and conversely, a persistent subaortic conus is accompanied by a subpulmonic location of the ventricular septal defect.

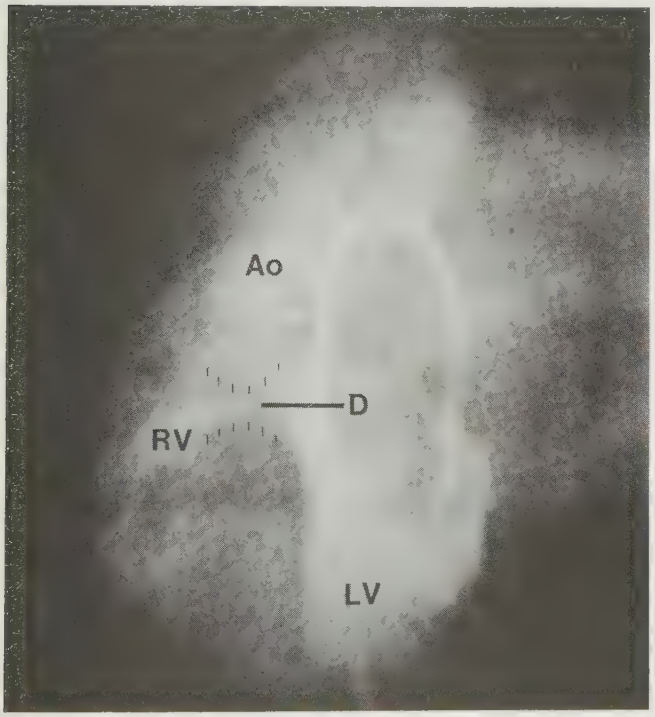

Fig. 72–6. Left ventriculogram in the long axial oblique view in a patient with double-outlet right ventricle and normally related great vessels. A persistent 15 mm Hg systolic gradient between the left ventricle (LV) and right ventricle (RV) present, along with angiographic suggestion of a restrictive subaortic ventricular septal defect (D). At operative repair, superior enlargement of the ventricular septal defect was required to create a nonobstructive tunnel between the left ventricle and aorta (Ao).

PHYSIOLOGY

There are three primary determinants of the circulatory dynamics present in DORV, which result in a spectrum of physiologic profiles that may simulate those of a large ventricular septal defect, tetralogy of Fallot, or transposition of the great arteries. Neufeld proposed a physiologic classification of DORV based on presence or absence of pulmonary stenosis, with subcategorization of the group without pulmonary stenosis based on the relation of the ventricular septal defect to the great arteries and right ventricular outflow tracts.[39,40] Associated left-sided obstructive lesions, the third factor, are also of major importance in DORV, either manifest as coarctation of the aorta or mitral valve anomalies in the newborn, or as progressive subaortic stenosis during childhood.[41]

Pressure Relationships

In most cases of DORV, the ventricular septal defect is nonrestrictive, and the pressures are equal in the right and left ventricles. However, echocardographic study has demonstrated that a nonrestrictive ventricular septal defect should not be assumed to be a large defect, as up to 17% of interventricular communications may require enlargement at operative repair.[42] As the aorta and pulmonary artery both originate from the right ventricle, systolic pressures in the great arteries are equal in the absence of pulmonic or subaortic obstruction.

Pulmonic stenosis is common in DORV, with a reported frequency of 60 to 70% in large series.[30,43] Pulmonic stenosis occurs most frequently in association with a subaortic ventricular septal defect and will result in physiology similar to tetralogy of Fallot. Pulmonic stenosis occurs less frequently in the presence of a subpulmonic ventricular septal defect. Conversely, subaortic obstruction is recognized in approximately 3% of cases of DORV, resulting in a gradient between the right ventricle and aorta.[26] The combination of both pulmonary stenosis and subaortic obstruction

is recognized, and may result in severe ventricular hypertrophy in response to the suprasystemic ventricular pressure.[41]

OXYGENATION

Systemic arterial saturation in DORV will be determined by the magnitude of pulmonary blood flow and the degree of mixing or streaming of oxygenated and deoxygenated blood in the right ventricle. Pulmonary blood flow may be restricted by either pulmonary stenosis or elevated pulmonary vascular resistance, while the relative oxygen saturations in the aorta and pulmonary artery are determined, in part, by the relationship of the ventricular septal defect to the great arteries.

Restricted Pulmonary Perfusion

Severe valvar or subpulmonic obstruction will result in circulatory dynamics similar to tetralogy of Fallot. Systolic pressures in both ventricles and the aorta are equal, with a pressure gradient between the right ventricle and pulmonary artery. As effective pulmonary stenosis occurs most frequently in association with a subaortic ventricular septal defect, there may be preferential streaming of the oxygenated left ventricular blood to the aorta, resulting in an aortic saturation greater than pulmonary saturation. Frequently, however, there is mixing of both right and left ventricular blood with equalization of saturation in both great arteries. In many cases, the catheterization findings are indistinguishable from classic tetralogy of Fallot, with differentiation based on angiography, at which time the diagnosis of DORV with tetralogy is established.

Increased Pulmonary Perfusion

In the absence of significant pulmonary stenosis or elevated pulmonary vascular resistance, the architecture of the right ventricular outflow tract will significantly influence the degree of mixing or streaming of the output of the right and left ventricles. In cases with a subaortic ventricular septal defect, the magnitude of pulmonary flow depends on the ratio of the pulmonary and systemic resistances. Relatively normal pulmonary vascular resistance will be accompanied by marked elevation in pulmonary flow and a pulmonary artery saturation approximating that of the fully saturated aorta. The aortic saturation may exceed pulmonary saturation if left ventricular output is directed to the aorta and little mixing occurs within the right ventricle. The hemodynamic findings then simulate those of a typical ventricular septal defect. The diagnosis of DORV with subaortic ventricular septal defect is established by echocardiography or angiography, as the hemodynamic profile does not allow differentiation from a standard ventricular septal defect. The determination of ventricular septal defect position relative to the aorta based on oxygen saturation alone may be inaccurate, as Sridaromont reported that 40% of patients with subaortic ventricular septal defect and DORV had a pulmonary arterial saturation greater than aortic saturation.[30] The small number of patients with doubly committed and noncommitted ventricular septal defect demonstrated differential aortic and pulmonary saturations, although inadequate in sample size to permit conclusions regarding the position of the ventricular septal defect relative to the great arteries, based on oximetry.

The presence of a subpulmonic ventricular septal defect would appear to correlate with a pulmonary artery saturation exceeding aortic saturation, regardless of the presence or absence of pulmonary stenosis of pulmonary obstructive vascular disease. The oxygenated left ventricular blood recirculates through the ventricular septal defect to the pulmonary artery, establishing the parallel circulation of transposition of the great arteries. A variable degree of mixing may occur in the right ventricle, although cyanosis is present as systemic venous return is directed to the aorta.[44] Clinically, these patients resemble infants with transposition of the great arteries and ventricular septal defect, as both cyanosis and congestive heart failure occur in infancy, and may improve in response to balloon atrial septostomy. Pulmonary flow is determined by pulmonary vascular resistance, and the early onset of pulmonary obstructive vascular disease is recognized.[45] The catheterization diagnosis of DORV with transposition of the great arteries will define both the anatomic and hemodynamic status.

CLINICAL PRESENTATION

The clinical features of DORV are diverse, reflecting the spectrum of physiologic correlates associated with the relationship of the ventricular septal defect to the aorta, the presence or absence of pulmonary stenosis, and associated left-sided obstructive lesions. The presentation and subsequent diagnosis of DORV are usually established in the first months of life, although clinically nonmanifest forms of DORV have been reported.[46] Three clinical groups, reflecting the circulatory dynamics in DORV are recognized: subaortic or subpulmonic ventricular septal defect with pulmonary stenosis, presenting similarly to tetralogy of Fallot; subaortic ventricular septal defect without pulmonary stenosis, presenting as a large ventricular septal defect with pulmonary hypertension; and subpulmonic ventricular septal defect, resembling transposition of the great arteries. These clinical features are modified by the presence of left-sided obstructive lesions.

In 1984 through 1986 my colleagues and I evaluated 19 infants referred for the evaluation of congenital heart disease, in whom the diagnosis of DORV was subsequently established. The clinical features of this group and age at referral are summarized in Fig. 72–7. The diagnosis of DORV in this patient group was established (or confirmed) by echocardiography (n = 18), catheterization (n = 17), corrective surgery (n = 12), or autopsy (n = 4).

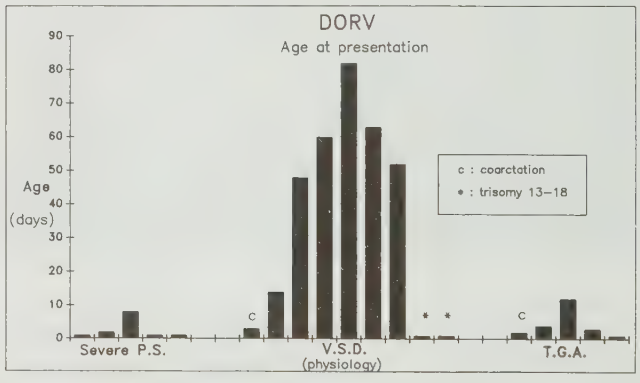

Fig. 72–7. Clinical features and age of referral of infants who underwent evaluation of congenital heart disease, in whom the diagnosis of DORV was subsequently established.

Subaortic or Subpulmonic Ventricular Septal Defect with Pulmonary Stenosis

The clinical features of this group simulate tetralogy of Fallot. Severe cyanosis in the newborn with pulmonary oligemia has recently resulted in uniform early referral of this defect for cardiac evaluation. Cyanosis was determined by the severity of obstruction to pulmonary blood flow, consisting of valvar pulmonic stenosis, subpulmonic stenosis, and obstructive mitral chordae in association with subpulmonic defects. Progressive subpulmonic stenosis was noted in four patients. Beyond the newborn period, cyanosis may be accompanied by hypercyanotic spells, failure to thrive, exertional dyspnea, and polycythemia.

On initial examination, a prominent right ventricular impulse and systolic thrill at the upper left sternal border may be palpable, with an associated harsh systolic murmur and single second heart sound on auscultation. Associated left-sided cardiac lesions are uncommon in this type of DORV.

Subaortic Ventricular Septal Defect without Pulmonary Stenosis

The clinical features in this group were typical of a large ventricular septal defect, with streaming of oxygenated left ventricular blood into the aorta. Minimal, if any, cyanosis was evident, with heart failure and failure to thrive the dominant clinical features. Referral for cardiac evaluation tended to occur later in this group, unless associated left heart lesions were present. Both patients with chromosomal abnormalities (trisomy 13, trisomy 18) and DORV had the ventricular septal defect in the subaortic position, without significant pulmonary stenosis.

A hyperdynamic precordial impulse was noted on initial examination, accompanied at times by a palpable thrill. A grade 3 to 4/6 holosystolic murmur and accentuated pulmonary component of the second heart sound were characteristic, followed by an apical diastolic rumble at the cardiac apex.

The anticipated development of pulmonary obstructive vascular disease in this setting will result in the reduction of pulmonary blood flow, accompanied by loss of the diastolic murmur, and attenuation of the systolic murmur. A very loud and single second heart sound and a diastolic decrescendo murmur of pulmonary insufficiency may evolve.

Subpulmonic Ventricular Septal Defect without Pulmonary Stenosis

The clinical features in this third group are similar to those of transposition of the great arteries with a ventricular septal defect. Variable degrees of cyanosis were manifest in this group, with arterial saturations ranging from 44 to 80%. The presence of coarctation or interruption of the aorta resulted in early clinical congestive heart failure, and referral in the first week of life. The most pronounced cyanosis was evident in the patients with pulmonic stenosis in association with DORV and a subpulmonic ventricular septal defect, accompanied by minimal congestive heart failure.

Initial examination demonstrated cyanosis, and congestive heart failure accompanied by cardiomegaly and diminished or absent femoral pulses, if coarctation was present. In the absence of pulmonary stenosis, tachypnea and pulmonary plethora were evident, accompanied by a loud pulmonary component of the second heart sound and a grade 3/6 systolic murmur and apical diastolic rumble; a systolic ejection click, severe cyanosis, and a systolic thrill and harsh murmur were the clinical hallmarks when severe pulmonary stenosis accompanied a subpulmonic ventricular septal defect.

RADIOGRAPHIC FEATURES

The roentgenographic findings in DORV are determined by the circulatory dynamics, and correlate with the clinical presentation. In general, cardiomegaly and pulmonary vascularity are determined by presence of pulmonary stenosis and the relative pulmonary vascular resistance.

Diminished pulmonary vascularity and a concave left upper heart border are observed when severe pulmonary stenosis accompanies a subaortic ventricular septal defect, as commonly observed in tetralogy of Fallot. In the absence of pulmonary stenosis, cases of DORV with ventricular septal defect demonstrate cardiomegaly, an enlarged main pulmonary artery, and increased pulmonary vascularity. The development of pulmonary obstructive vascular disease will result in reduced pulmonary vascularity, with enlarged proximal pulmonary arteries.

DORV with subpulmonary ventricular septal defect will resemble transposition of the great arteries on the chest roentgenogram, with increased pulmonary vascularity in association with cardiomegaly. In DORV with the aorta anterior and left, the "l-malposition" of the aorta may be recognized by the position of the great arteries, in association with increased pulmonary markings (Fig. 72–8).

The radiographic features of DORV provide corroboration of the clinical findings. Differentiation from other forms of congenital heart disease, however, is based on echocardiography and cardiac catheterization.

ELECTROCARDIOGRAPHIC FEATURES

Although early electrocardiographic studies suggested that the diagnosis of DORV could be suspected prior to cardiac catheterization based on certain aspects of the electrocardiogram,[39,47] this was not substantiated by subsequent studies.[48,49] Electrocardiographic abnormalities are present in most patients with DORV, although none can be considered pathognomonic for this group of defects. Left axis deviation with a counterclockwise frontal plane loop may occur due to displacement of the bundle of His, posterior to the ventricular septal defect.[50] Abnormal early activation of the posterior–inferior left ventricle will result, manifest as left axis deviation and a counterclockwise frontal plane loop. This is an inconstant finding, reported in 6 to 50% of cases of DORV,[47,49] also present in other forms of complex congenital heart disease.

Right ventricular hypertrophy is invariably present beyond the newborn period, reflecting the systemic work of the right ventricle. Left ventricular forces may be normal, or increased in the patient with a subpulmonic ventricular septal defect or restrictive left ventricular outflow tract. Right atrial enlargement may be more frequent in association with pulmonary stenosis, while left atrial enlargement may indicate increased pulmonary blood flow with an intact atrial septum.

First-degree atrioventricular conduction delay is common, particularly when a complete atrioventricular septal defect is present in association with DORV. Abnormalities of atrial rhythm may be

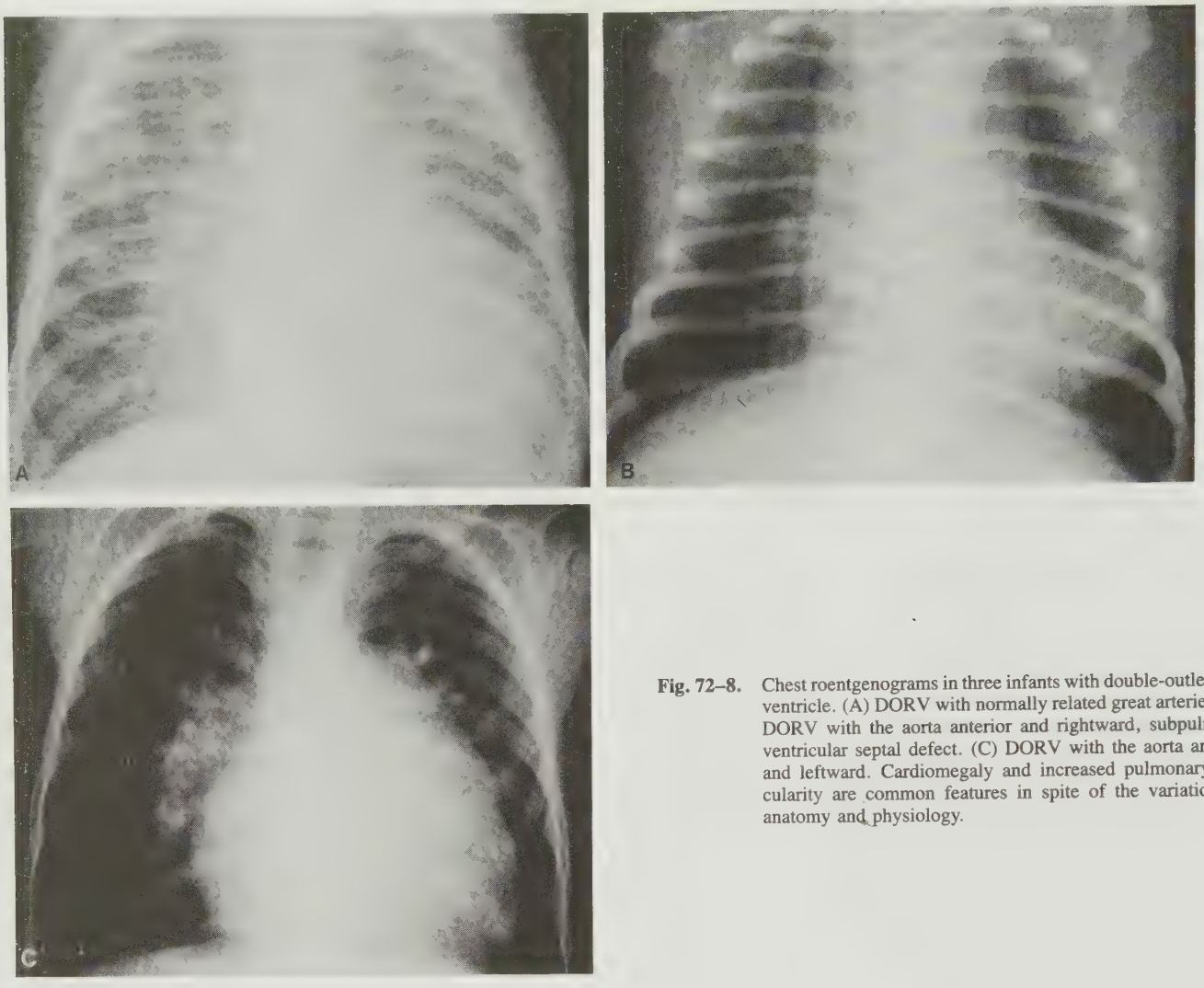

Fig. 72–8. Chest roentgenograms in three infants with double-outlet right ventricle. (A) DORV with normally related great arteries. (B) DORV with the aorta anterior and rightward, subpulmonic ventricular septal defect. (C) DORV with the aorta anterior and leftward. Cardiomegaly and increased pulmonary vascularity are common features in spite of the variations of anatomy and physiology.

present due to atrial enlargement or abnormal sinus node location, if associated abdominal heterotaxia is present.[51]

ECHOCARDIOGRAPHY

The initial echocardiographic studies of DORV were based on M-mode demonstration of mitral-semilunar discontinuity.[52] Subsequent recognition of the subjective nature of this measurement, and a high degree of false-negative and false-positive results, resulted in limited successful application of M-mode echocardiography in the diagnosis of DORV.[53] Further limitations were imposed by the complexities of great artery and atrioventricular valve relations, and inability to define the location of the ventricular septal defect.

Diagnostic criteria to establish the two-dimensional echocardiographic diagnosis of DORV have been proposed, in accordance with the various definitions of DORV.[31,54–55] Because of the extreme heterogeneity of this group of congenital heart defects, standardization remains difficult, with accurate anatomic description required in each case. In general, the following features should be established by echocardiographic examination:

1. The primary commitment of both great arteries to the right ventricle;
2. The spatial relationship of the great arteries;
3. The location of the ventricular septal defect and relation to the semilunar valves; and
4. The presence and type of associated anomalies.

Both parasternal long axis and apical/subcostal imaging will provide documentation of primary origin of both great arteries from the right ventricle,[31,56] while imaging the bifurcation of the pulmonary arteries from the parasternal short axis or subxiphoid views will define the relation of the great arteries.[57] The position of the ventricular septal defect relative to the outflow tracts is best defined from multiple long- and short-axis sweeps (Fig. 72–9).

Increased recognition of the prevalence of associated anomalies in DORV has evolved with two-dimensional echocardiography. In particular, the anatomic variations of atrioventricular valve straddling and override in association with DORV have been elucidated.[58] Also, as previously discussed, anticipation of a potentially restrictive ventricular septal defect following surgical repair has become increasingly frequent.[31]

Two-dimensional echocardiography has advanced the diagnos-

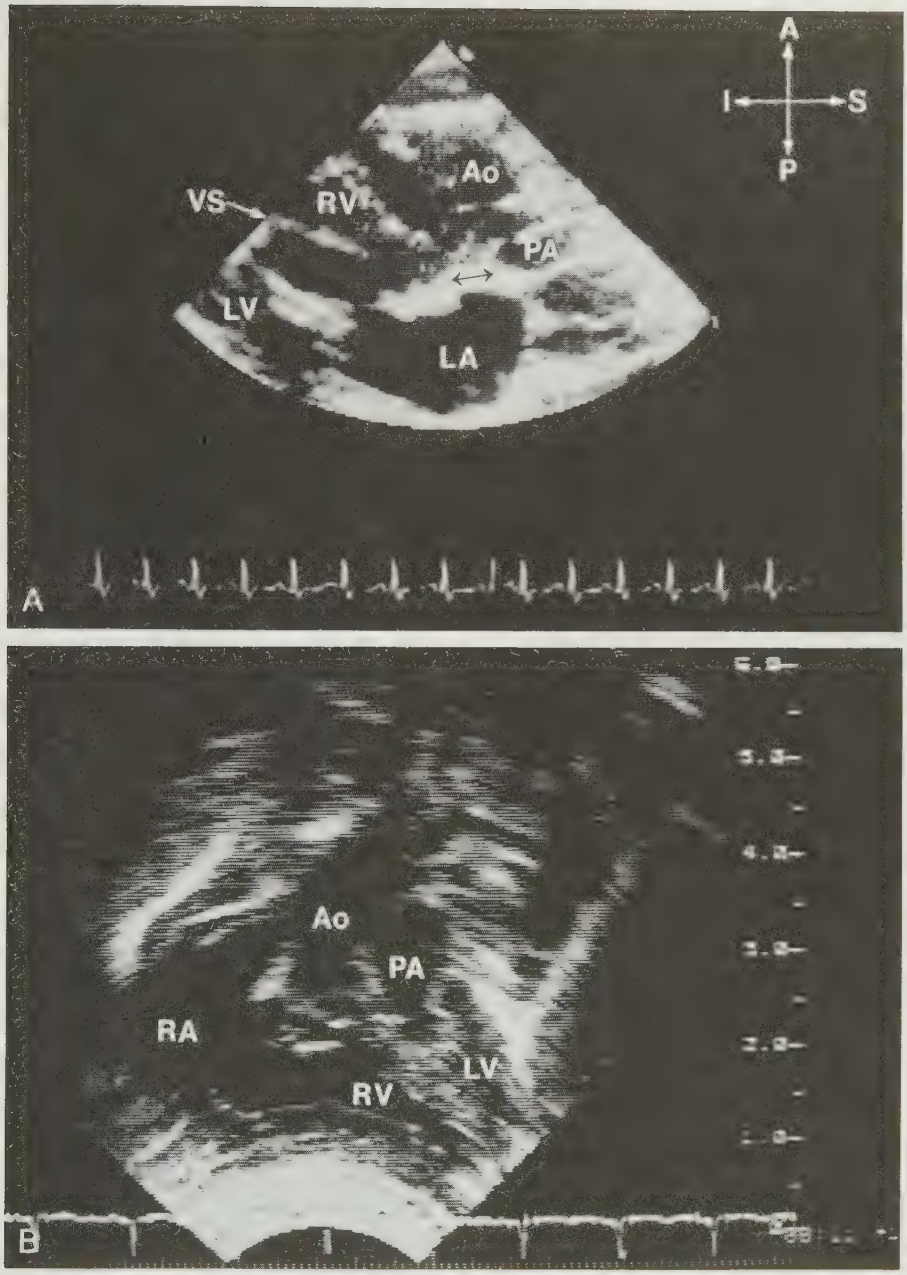

Fig. 72–9. Echocardiographic features of double-outlet right ventricle. (A) Parasternal long axis view, with commitment of both great arteries to the anterior right ventricle (RV), and a parallel course of the posterior pulmonary artery (PA), and anterior aorta (Ao). A large subpulmonic ventricular septal defect is present, with a subpulmonic conus (arrows) separating the mitral valve (MV) from the pulmonary artery. (B) Subcostal four-chamber imaging, demonstrating origin of both great arteries from the right ventricle (RV). The aorta (Ao) is identified by the specific branching pattern. LA = left atrium; RA = right atrium; LV = left ventricle; VS = ventricular septum.

tic recognition of DORV, and differentiation from other conotruncal abnormalities. The prevalence of associated anomalies must be considered during examination, with the perspective that DORV is a definition only of the ventriculoarterial connection.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

Cardiac catheterization and angiography, in conjunction with two-dimensional echocardiography, provide complete and precise anatomic and hemodynamic delineation in the various forms of DORV. Prior to surgical intervention, the following aspects of anatomy in DORV require definition:

1. Abdominal situs and segmental connections;
2. Atrioventricular-valve morphology and insertion;
3. Relative left ventricular volume;
4. Size and location of the ventricular septal defect;
5. Spatial relationship of the great arteries;
6. The presence of pulmonic or subaortic obstruction; and
7. Aortic arch anatomy.

The hemodynamics of the various forms of DORV have previously been discussed. Although many aspects may be predicted from clinical presentation and echocardiography, important details at catheterization deserve emphasis. In DORV with subaortic ventricular septal defect and severe pulmonic stenosis, left-sided obstructive lesions are rare. However, left ventricular volume may be deficient, due to limited pulmonary venous return, and the primary systolic function of the right ventricle (Fig. 72–3). Although primarily recognized in tetralogy of Fallot, relative hypoplasia of the left ventricle may also occur in DORV.[59,60]

DORV with a subaortic ventricular septal defect without pulmonary stenosis should be approached similarly to a large ventricular septal defect with associated pulmonary hypertension. Evaluation of pulmonary vascular resistance and reactivity are of paramount importance. In addition, relative restriction of the ventricular septal defect or of the subaortic conus occur most frequently in this form of DORV, and must be excluded before surgery.

The patient with a subpulmonic ventricular septal defect and DORV presents the greatest complexities in hemodynamic evaluation. The high incidence of associated left-sided obstructive lesions requires systematic evaluation, along with evaluation of pulmonary vascular resistance due to the potential for early advanced pulmonary obstructive vascular disease. The degree of intracardiac mixing afforded by the ventricular septal defect requires individual case consideration, although the relative ratio of pulmonic to systemic flows appears to determine the effective mixing of the two circuits.[61]

Neufeld et al., in their physiologic categorization of DORV, recognized that the position of the ventricular septal defect was a major determinant in the streaming of oxygenated left ventricular blood.[9] The effective mixing of the two circulations can only be determined by direct measurement of the pulmonary and aortic saturations, as marked streaming may occur in the right ventricle. Increased pulmonary flow with an aortic saturation less than 70%, or a pulmonary saturation 10% greater than aortic, indicate the potential for improvement following balloon or blade atrial septectomy, in the presence of a restrictive atrial septal defect.[62]

The angiographic features of DORV were first reported by Carey and Edwards in 1965.[63] The following diagnostic criteria were proposed: opacification of both great arteries following right ventriculography, a similar horizontal plane of both the aortic and pulmonary valves, frequent anterior malposition of the aorta, and the presence of a "filling defect" dividing the two outflow tracts (Fig. 72–10). These criteria have, in general, proved valid, modified by the subsequent description of the angiographic features of mitral-semilunar discontinuity and the development of biplane angiography.

In DORV, biplane axial angiography must be performed in both ventricles to define the ventricular septal defect and its relation to the great arteries (Fig. 72–11). As stated by Elliot et al., "DORV is a difficult diagnosis to make correctly, but in no other entity is the value of axial angiography more apparent."[64] A left ventriculogram in the long axial oblique projection will define the relation of the anterior mitral valve leaflet to the semilunar valves, and the location, size, and number of ventricular septal defects (Fig. 72–12). Aortography is also requisite to define coronary artery anatomy and to exclude coarctation of the aorta. Coronary artery anomalies are most frequently recognized in patients with DORV and pulmonary stenosis, primarily originating in the left anterior descending artery from the right coronary artery as in classic tetralogy of Fallot,[65] and requires definition before surgical repair involving a ventriculotomy is recommended.

CARDIAC ANOMALIES ASSOCIATED WITH DOUBLE-OUTLET RIGHT VENTRICLE

The physiology and surgical anatomy of DORV are frequently complicated by the presence of additional congenital heart defects. The overall prevalence of associated defects in large series are summarized in Table 72–1. DORV occurs as the only major lesion in less than half of all cases, with frequent associated anomalies of the ventricles, atrioventricular valves, and abdominal situs.[21] However, the association of these defects with the various forms of DORV would not appear to be a random event, as the occurrence of a specific associated defect tends to correlate with the presence of a specific relation between the great arteries and ventricular septal defect.

Obstruction of the Pulmonary Circulation

The various forms of valvar and subvalvar pulmonary stenosis represent the most common anomaly associated with DORV. Variable degrees of pulmonary stenosis occur in 60 to 70% of cases of DORV with a subaortic ventricular septal defect.[26,42] However, in association with a subpulmonic ventricular septal defect and DORV, pulmonary stenosis was not present in certain series,[26] and much less frequent in others. Most recognized cases of persistent common atrioventricular canal with DORV are accompanied by pulmonary stenosis.[66]

Obstructions of the Systemic Circulation

The second common group of cardiac anomalies associated with DORV are generally considered "left heart" obstructive lesions. Obstruction to systemic blood flow in DORV may occur because of a restrictive ventricular septal defect, subaortic or aortic valve stenosis, and coarctation or interruption of the aortic arch. In general, conditions producing obstruction to systemic outflow are more frequently associated with a subpulmonary location of the ventricular septal defect.[67] Also, in contrast to pulmonic stenosis,

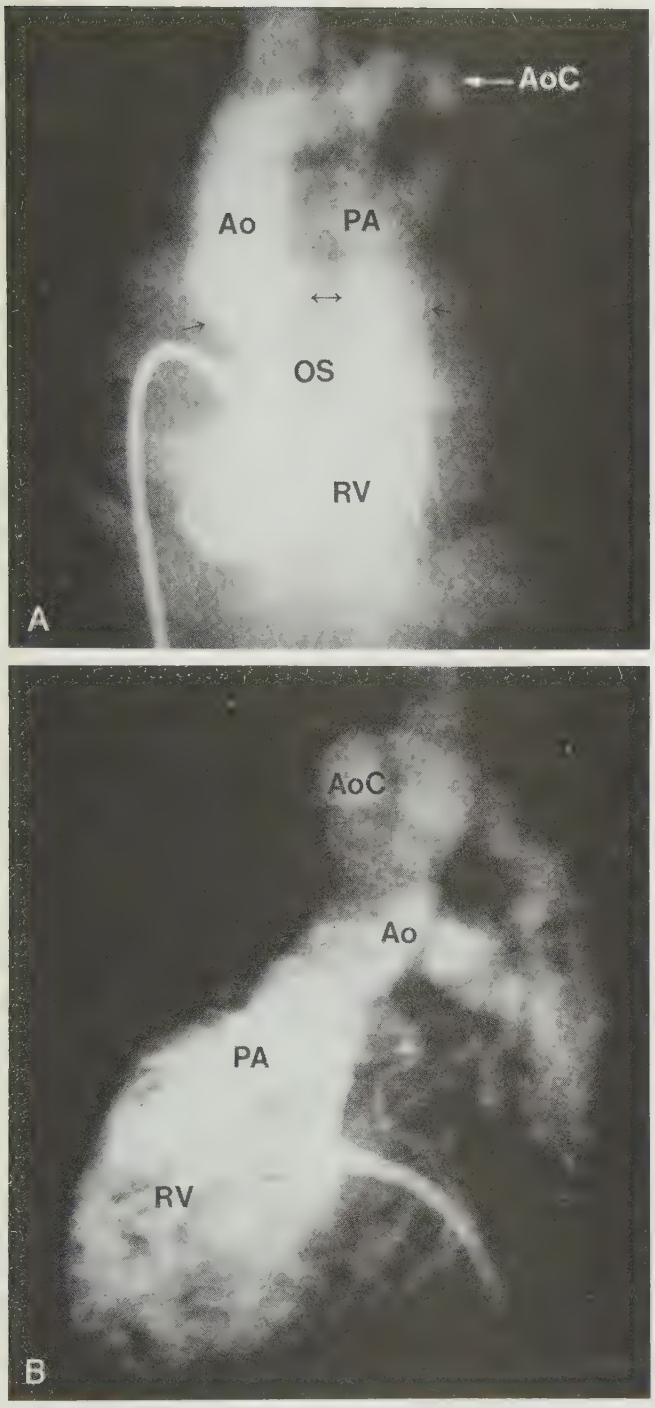

Fig. 72–10. Double-outlet right ventricle with side-by-side great artery relationship and subpulmonic ventricular septal defect. A) The classic angiographic features described by Carey and Edwards are illustrated: 1) filling of both great arteries (Ao and PA) during right ventriculography (RV); 2) a similar horizontal plane of both semilunar valves (arrows); and 3) a filling defect between the great arteries (outlet septum, OS). B) Interruption of the aorta was also present in this case, and an ascending–descending aortic conduit is visualized (AoC) in the lateral view.

this group of defects considerably influences the prognosis of the patient with DORV.

Restriction to left ventricular outflow may be due to a small ventricular septal defect or incorporation of a portion of the atrioventricular valve apparatus into the ventricular septal defect.[28] There is increased recognition of these anatomic variants, which are of major surgical importance, in the current decade, due to the advances of echocardiography.

Muscular hypertrophy of the aortic conus and infundibular septum may result in subaortic stenosis.[68] The potential for progressive subaortic hypertrophy and obstruction may be suggested by angiography before the development of a systolic gradient. Aortic valve stenosis in DORV most frequently is documented in the setting of mitral valve abnormalities.[33]

Coarctation of the aorta represents the most frequent left-sided obstructive lesion in association with DORV.[67] Some authors have noted a definite correlation of coarctation with a subpulmonic ventricular septal defect,[26] although aortic arch abnormalities may occur with any form of DORV (Fig. 72–10).

Left Ventricular Inflow Anomalies

Abnormalities of pulmonary venous return and the mitral valve represent severe but less frequent complexities associated with DORV. No specific correlation between left ventricular inflow restriction and location of a ventricular septal defect is recognized. Restricted or atretic mitral inflow does correlate with hypoplasia of the left ventricle and aortic outflow[66] (Fig. 72–13). As noted, a number of cases of intact ventricular septum in association with DORV have been reported, most in context of mitral stenosis or atresia. Hypoplasia of the left ventricle may also occur when decreased pulmonary blood flow is accompanied by a large atrial septal defect, and a small ventricular septal defect.

Override of either atrioventricular valve annulus or straddling of chordae occurs relatively frequently in DORV. This malalignment of the atrioventricular valves may be of major surgical importance, and requires delineation by two-dimensional echocardiography.[58,68]

Coronary Arterial Patterns

The initial descriptions of coronary artery anatomy in DORV suggested that the origin and course of the two main coronary arteries were essentially identical to those of the normal heart.[69,70] Elliot et al.[69] reported one case of anomalous origin of the right coronary artery from the left main coronary artery, and another case in which two anterior descending coronary arteries were present, with bilateral origin from the right and left coronary arteries.

Sridaromont et al. reported five cases of anomalous origin of the left anterior descending artery from the right coronary artery, all in patients with a subaortic ventricular septal defect and pulmonary stenosis in association with DORV.[30] This coronary anomaly, typically associated with tetralogy of Fallot, emphasizes the anatomic and physiologic continuity of the spectrum of conotruncal abnormalities.

In d-transposition of the aorta and subpulmonary ventricular septal defect, coronary artery anatomy is similar to that observed in transposition of the great arteries.[71] The right coronary artery originates from the posterior sinus of Valsalva, with origin of the left main coronary artery from the left sinus. Wilcox et al.[3] noted a frequent coronary anomaly in DORV, regardless of the origin

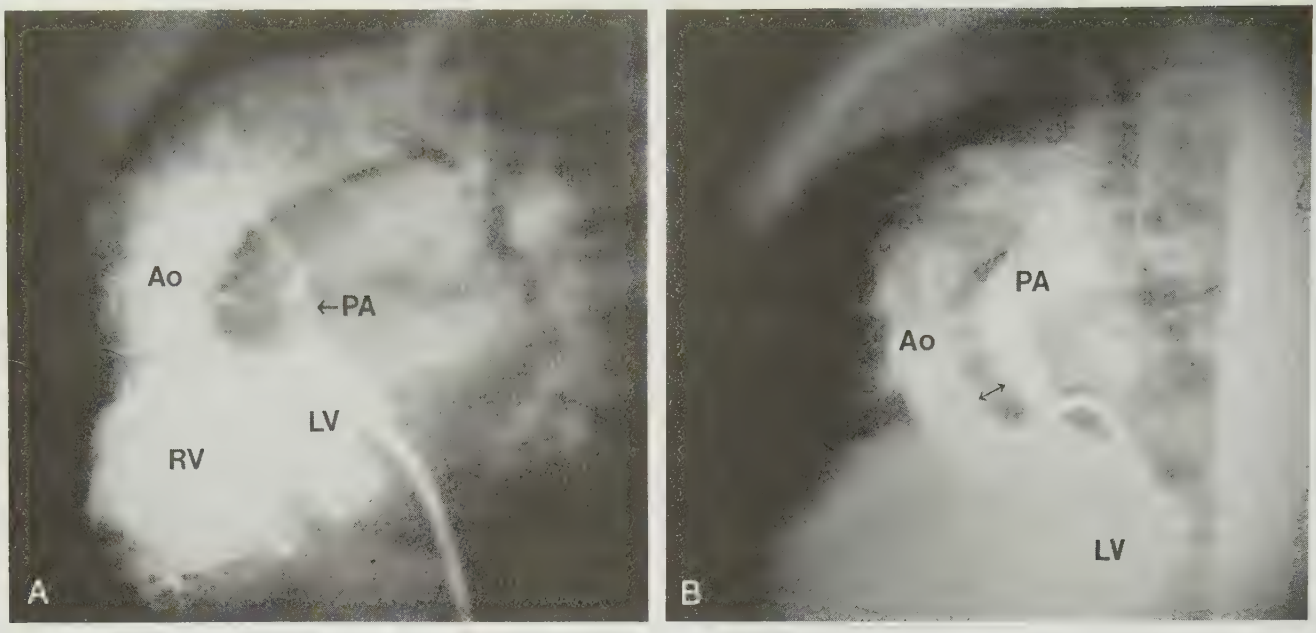

Fig. 72–11. Lateral-projection right ventriculogram (A) and left-anterior-oblique left ventriculogram (B) demonstrating persistence of a bilateral conus (arrows), with a poorly expanded subpulmonic conus. However, the posterior pulmonary artery (PA) is committed to the left ventricle (LV), and thus this case would not be classified as double-outlet right ventricle. The absence of arterial override was confirmed at surgical repair. The importance of axial biplane angiography, and the occurrence of a bilateral conus in other forms of congenital heart disease are emphasized. Ao = aorta; RV = right ventricle.

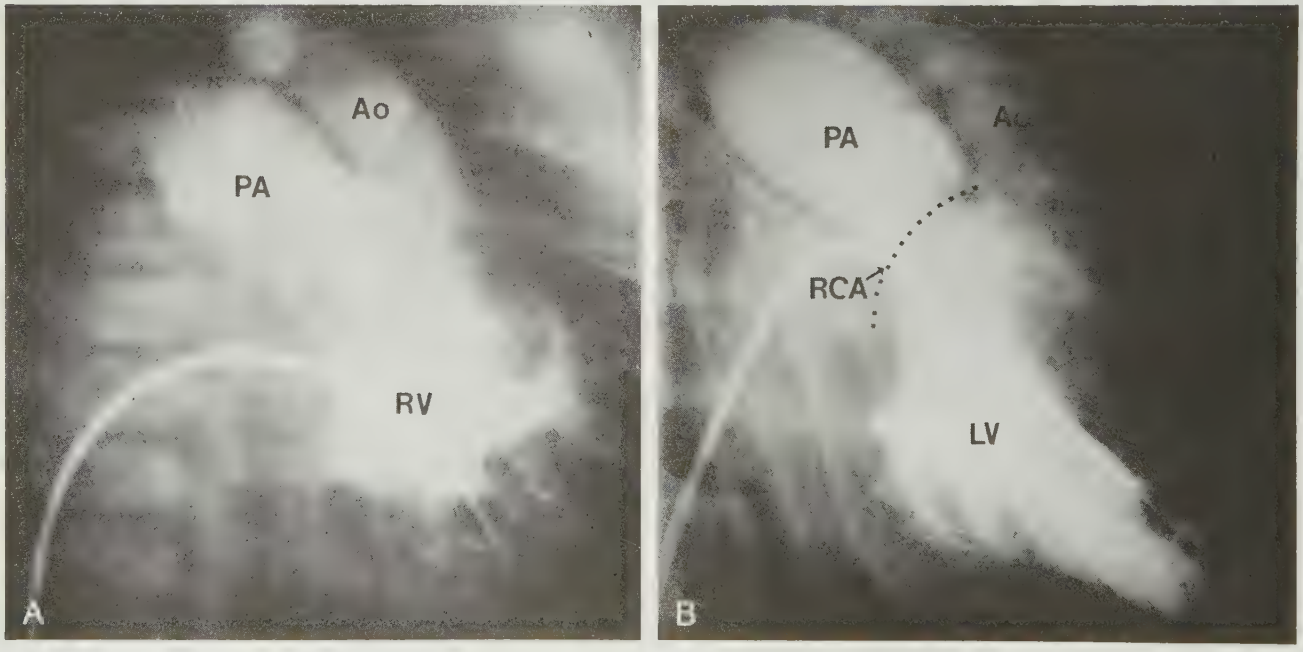

Fig. 72–12. Double-outlet right ventricle with levomalposition of the great arteries and subpulmonic ventricular septal defect. A) Right ventriculogram (RV) in the frontal projection demonstrating enlargement of the pulmonary artery (PA), and the leftward origin of the aorta (Ao). B) Right-anterior-oblique-projection left ventriculogram (LV). The course of the right coronary artery (RCA), crossing the anterior right ventricular outflow tract, is illustrated.

Table 72–1. Prevalence of Cardiac Anomalies Associated with Double-Outlet Right Ventricle

Reference #	*Sridaromont (30)*	*Lev (2, 66)*	*Sondheimer (26)*	*Cameron (33)*	*Zamora (67)*
Total # of DORV	62	133	87	27	33
Pulmonary Stenosis:	29	55	28	12	6
VSD:					
intact	2	6		8	2
restrictive	1				2
Systemic Obstruction:					
Coarctation	1		11		10
Aortic stenosis		16	2	8	3
Sub-aortic stenosis	2	4			10
Mitral Valve Anomalies:					
Atresia	1	3	4	13	3
Stenosis	2	2	1		4
Straddle	1			4	2
Miscellaneous:					
ASD	16			10	7
TAPVR		2	1	4	1
L-SVC				3	3
PDA	10			18	
AV Canal	4	11	5	2	

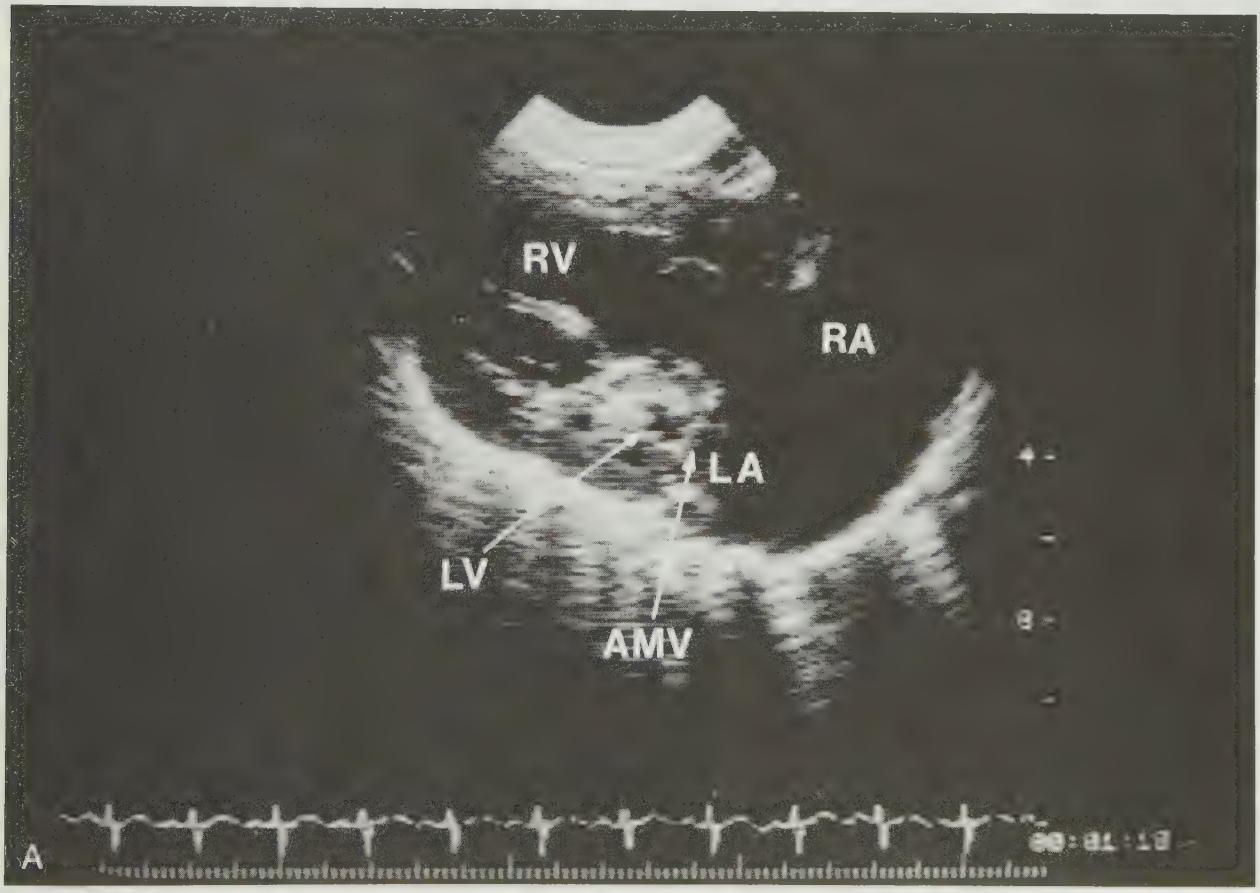

Fig. 72–13. Subcostal four-chamber echocardiography in a patient with double-outlet right ventricle, mitral atresia, subaortic ventricular septal defect, and normally related great vessels (Ao and PA). A) Posterior imaging, demonstrating the atretic mitral valve (AMV), hypoplastic left ventricle (LV), left atrium (LA), right atrium (RA) and right ventricle (RV).

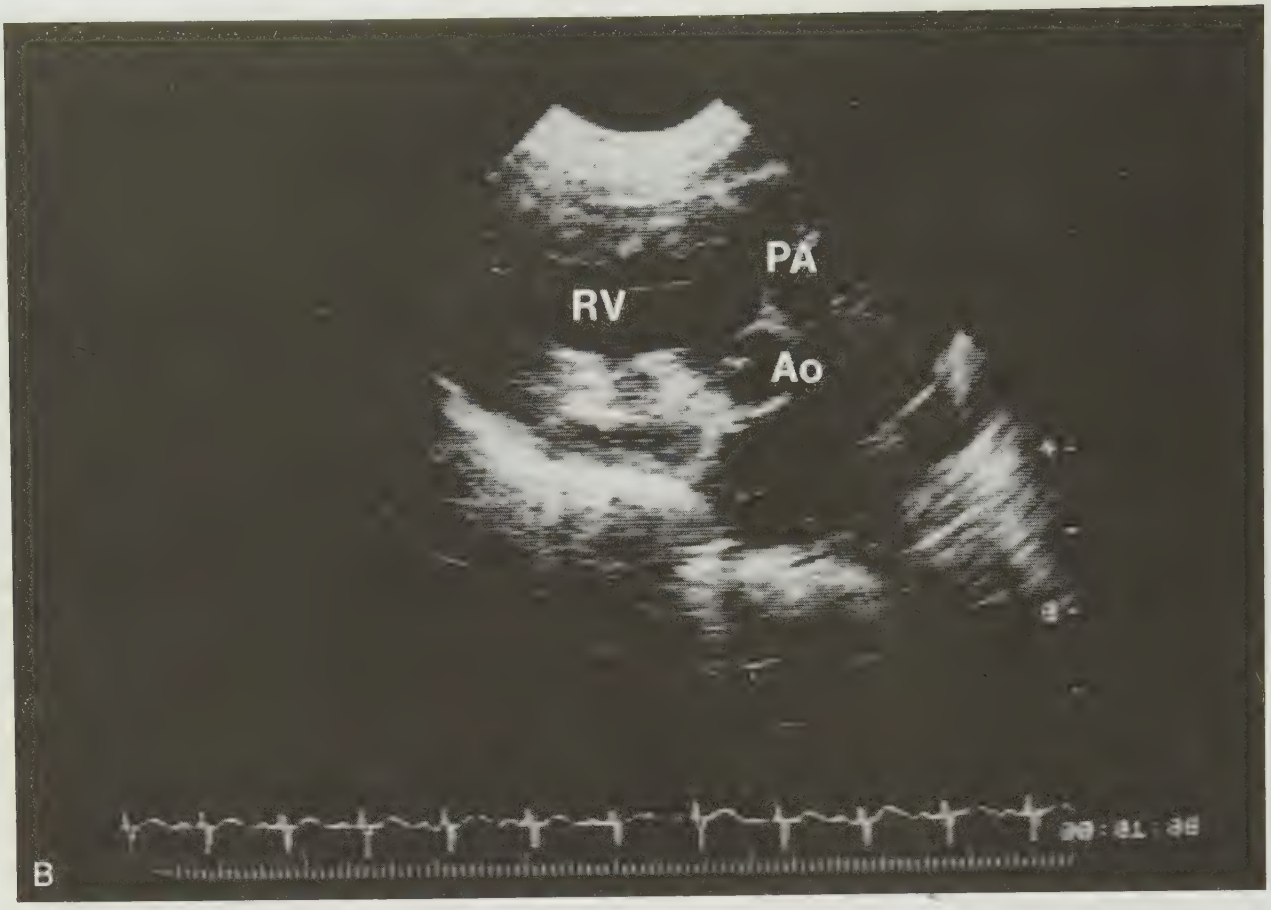

Fig. 72–13 *continued.* B) Anterior imaging, with moderate hypoplasia of the ascending aorta (Ao), and an enlarged pulmonary artery (PA), both originating from the right ventricle (RV). A subaortic ventricular septal defect provides the only communication with the left ventricle. Long-term palliation has been attained in this patient following a modified Norwood procedure.

of the right coronary artery (i.e., from the anterior or posterior sinus): an anterior origin of the left anterior descending artery, with a subsequent course inferior to the pulmonary annulus in the ventricular free wall, which could preclude right ventriculotomy.

In l-malposition of the aorta with DORV, the right coronary artery courses immediately beneath the pulmonary annulus. The subpulmonary conus tends to be poorly expanded in this anatomy, resulting in infundibular and annular stenosis.[72] The surgical approaches to pulmonary outflow reconstruction must be based on anticipation of this anatomy.

A number of patterns of coronary arterial anatomy have been recognized in patients who have had successful arterial transfer in their repair of DORV.[73] However, given the frequency and variability of this anatomy, preoperative angiographic definition of the coronary arteries would appear warranted, regardless of the type of repair used (Fig. 72–14).

CONDUCTION SYSTEM

The course of the atrioventricular node and His-Purkinje system in DORV with atrioventricular concordance is similar to that described for isolated perimembranous ventricular septal defects.[74] The atrioventricular node begins between the coronary sinus and medial leaflet of the tricuspid valve, with the penetrating portion of the His bundle passing through the central fibrous body and subsequently beneath the crest of the ventricular septal defect. This relatively normal course is anticipated, as the development of the atrioventricular node and bundle branches are related primarily to the endocardial cushions and posterior ventricular septum, not the bulbus cordis.[75] In subaortic, subpulmonary, or doubly committed defects with a caudal muscular border, the conduction tissues are further displaced away from the superior margin of the defect. Thus, if surgical repair requires enlargement of the ventricular septal defect, this may be done at the apical aspect of the interventricular communication, and include the outlet septum.[76] The exception to this rule occurs when a muscular inlet defect occurs in association with DORV, when a superior course of the conduction tissues is recognized.[77]

COMPLEX ANATOMY ASSOCIATED WITH DOUBLE-OUTLET RIGHT VENTRICLE

Dextrocardia, Atrioventricular Discordance, and Double-Outlet Right Ventricle

Situs solitus of the atria and abdominal viscera, accompanied by atrioventricular discordance and dextrocardia are recognized to occur in conjunction with DORV.[77] The discordant ventricular loop

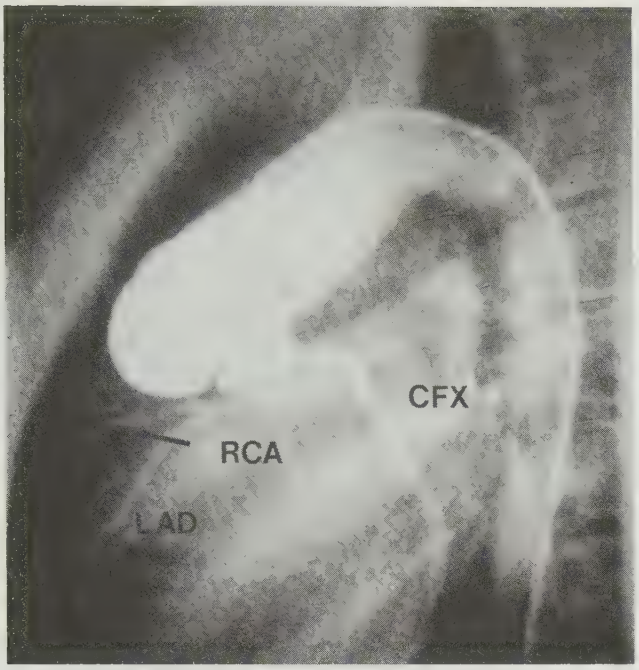

Fig. 72–14. Aortogram in the lateral view, demonstrating a single coronary artery arising from the left sinus of Valsalva in association with double-outlet right ventricle and a superior–anterior ventricular relationship (see Fig. 72–15). A dominant circumflex (CFX) artery courses posteriorly in the usual course, in addition to anterior distribution of the right coronary artery (RCA) and left anterior descending (LAD) artery.

(''l-loop'') is accompanied by levomalposition of the great arteries, with a persistent bilateral conus and origin of both great arteries from the morphologic right ventricle. Classification of this anatomy as ''situs solitus/l-loop/d-DORV'' has been suggested to emphasize the right and anterior position of the aorta.[78] The ventricular septal defect is in a subpulmonic position, usually accompanied by both valvar and subvalvar pulmonic stenosis.

Angiography will define the morphologic right and left ventricles and the relation of the great arteries (Fig. 72–15). Surgical correction of this constellation of defects was first reported by Kiser et al., by closure of the ventricular septal defect, transection of the pulmonary artery, and use of an extracardiac conduit to establish continuity between the morphologic left ventricle and pulmonary artery.[79]

Superior–Inferior Ventricles with Double-Outlet Right Ventricle

A superior–inferior relationship of the ventricles, with origin of both great arteries from the superior right ventricle, represents an additional complexity in the spectrum of DORV.[80] A variety of segmental connections and arterial relationships have been described in this complex, thus categorization of this complex is not appropriate. Inherent to this form of DORV is a ventricular septal defect located in the inlet septum, frequently associated with straddling of the atrioventricular valve chordae, which may preclude corrective surgical repair[19] (Fig. 72–16).

Single Atrioventricular Valve Connection with Double-Outlet Right Ventricle

Double-outlet right ventricle has been reported in association with the various atrioventricular valve abnormalities, reflecting the embryonic nature of this defect. A common atrioventricular canal defect in association with DORV and pulmonary stenosis is the most common of these rare constellations of congenital heart defects, which may be accompanied by total anomalous pulmonary venous return and asplenia.[66,81] DORV has also been reported in association with tricuspid atresia, double-chambered right ventricle and the trisomy 18 syndrome.[82–85]

NATURAL HISTORY

The anticipated clinical course of the patient with DORV who does not undergo surgery is determined by the associated physiology, and the presence and severity of associated congenital heart defects. DORV with a large subaortic ventricular septal defect will result in the development of pulmonary obstructive vascular disease, at least as rapidly as in the patient with a large, isolated ventricular septal defect.[86] Sondheimer reported four deaths and two additional cases of advanced pulmonary obstructive vascular disease in 18 patients with DORV and subaortic ventricular septal defect evaluated between 1956 and 1975.[26] In the same series, the natural history of DORV with subaortic ventricular septal defect and pulmonary stenosis was the most favorable, with long-term survival and patient-management protocols similar to those used in tetralogy of Fallot. Long-term survival, either by palliative systemic-pulmonary shunting or corrective surgery, remains the anticipated course in this group.

As DORV with subpulmonary ventricular septal defect is infrequently accompanied by pulmonic stenosis, the early development of pulmonary obstructive vascular disease, as in patients with transposition of the great arteries and ventricular septal defect, is anticipated. This may be compounded by the presence of left-sided obstructive lesions, in particular, coarctation of the aorta, which remains associated with a high rate of early mortality.[43,87]

CORRECTIVE SURGERY FOR DOUBLE-OUTLET RIGHT VENTRICLE

Analysis of the results of surgical correction of DORV is complicated, due to the multiple morphologic subsets of this defect, associated congenital heart defects, and differing surgical protocols. The successful intracardiac repair of DORV was first performed by Kirklin in 1957, creating an interventricular tunnel to connect the left ventricle to the aorta via the ventricular septal defect.[88] The establishment of left ventricle–aortic continuity in the patient with a subaortic ventricular septal defect has remained the classic form of repair of DORV since its inception 30 years ago. However, the surgical approach to DORV with subpulmonic ventricular septal defect has remained controversial since the first successful repair in 1967.[89]

As proposed by Lev, and recently analyzed by Kirklin, the commitment of the ventricular septal defect to the great arteries and location of the ventricular septal defect in the interventricular septum are the crucial variables in the repair of DORV.[2,11,90] The surgical results for DORV with a subaortic or doubly committed

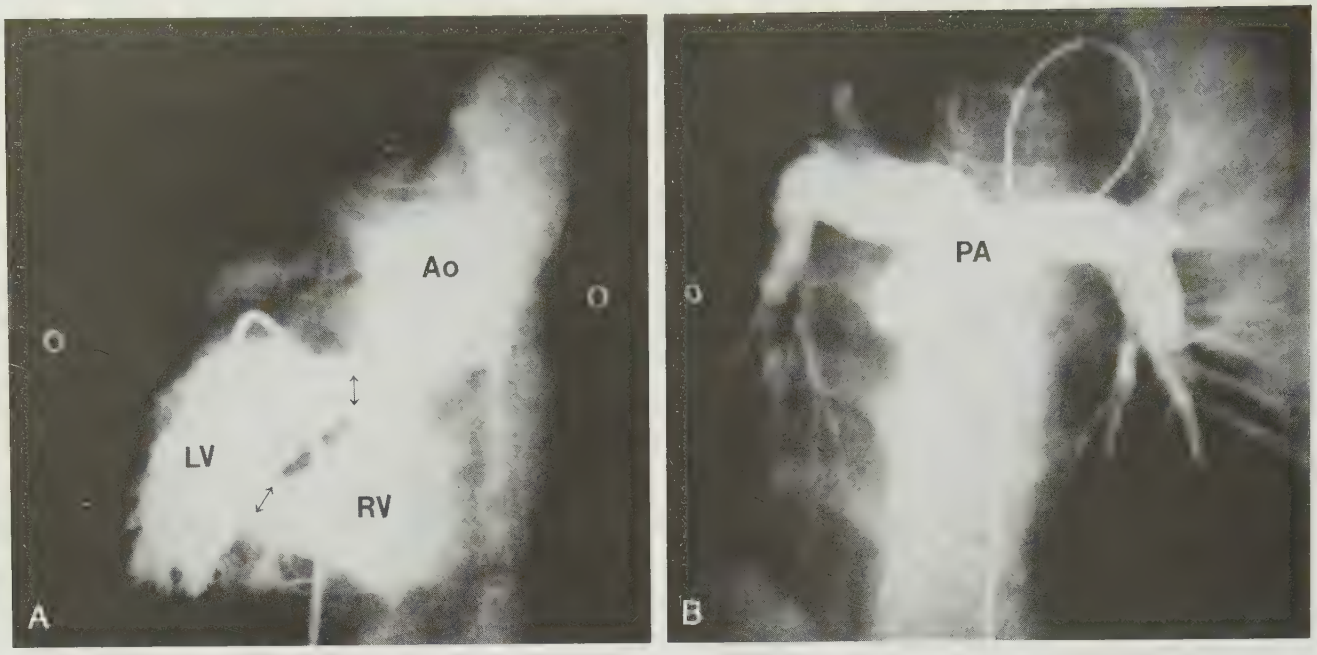

Fig. 72–15. Double-outlet right ventricle with dextrocardia, atrioventricular discordance, and associated pulmonary valve atresia. (A) Frontal-view left ventriculogram (LV) demonstrating two ventricular septal defects (arrows), and an anterior and left origin of the aorta (Ao) from the right ventricle (RV). (B) Pulmonary arteriogram (same projection) illustrating alignment of the pulmonary annulus (PA) above the morphologic right ventricle. This case is classified as DORV, as both great arteries are aligned above the right ventricle, although only the aorta is connected to the right ventricle at the subaortic conus.

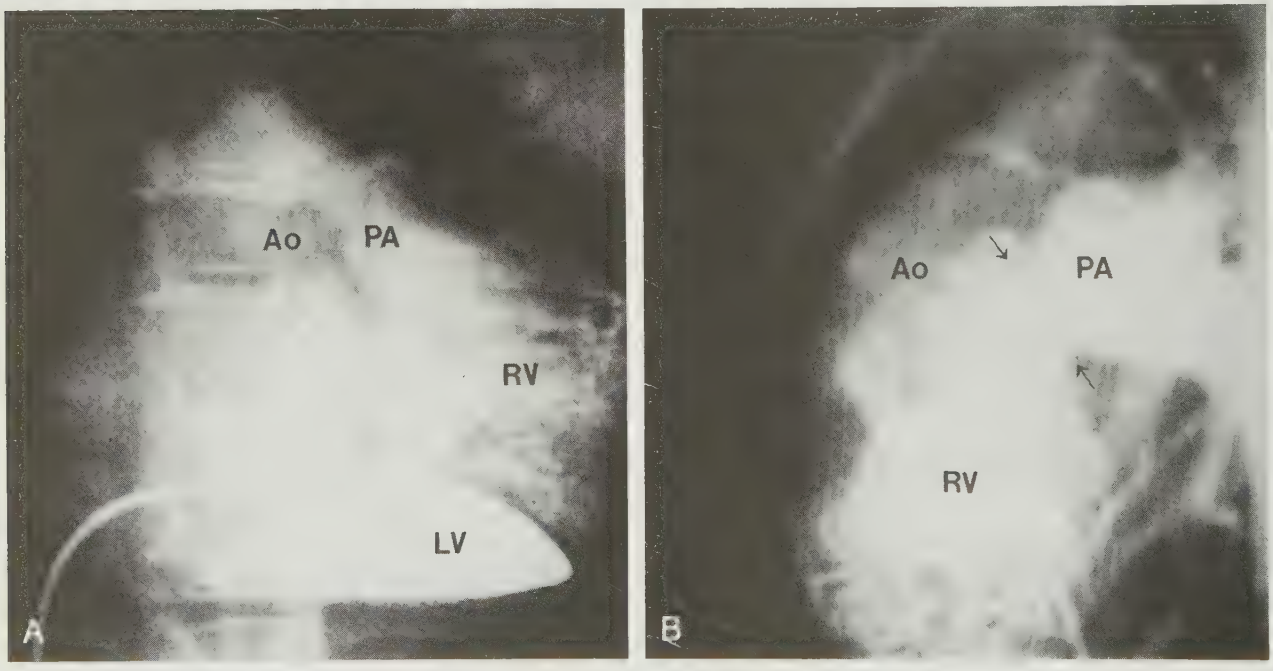

Fig. 72–16. Double-outlet right ventricle with an inferior and hypoplastic morphologic left ventricle, and a superior right ventricle. (A) Frontal-view left ventriculogram (LV), demonstrating multiple ventricular septal defects, which provide the only outlet for this chamber. Ao = aorta; PA = pulmonary artery; RV = right ventricle. (B) Lateral view of the superior right ventricle (RV), demonstrating coarse trabeculation, with an anterior origin of the aorta (Ao) and a posterior pulmonary artery (PA), which had previously been banded (arrows).

ventricular septal defect have progressively improved; currently, a low operative mortality and excellent long-term results are anticipated. However, the multiple surgical approaches to DORV with a subpulmonic or noncommitted ventricular septal defect emphasize the complexity of this repair, with less favorable results.

Double-Outlet Right Ventricle with Subaortic Ventricular Septal Defect

In the absence of significant associated congenital heart disease, the proximity of the ventricular septal defect to the aorta is of major importance in the establishment of continuity between the ventricular septal defect and the subaortic outflow tract.[2] Our current protocol, that reported by Kirklin et al., would favor primary intracardiac repair of DORV with subaortic ventricular septal defect before 12 months of age, in the absence of significant associated congenital heart disease.[11] Pulmonary artery banding, as a preliminary procedure, is not indicated in uncomplicated forms of DORV.

Although an initial operative mortality of 22% was reported in DORV with subaortic ventricular septal defect,[91] current experience would predict long-term survival to exceed 95%, with an excellent functional result.[92] The enlargement of a restrictive ventricular septal defect does not appear to be an incremental surgical risk factor; however, this must be recognized preoperatively.[93] Within this morphologic subset, the presence of severe mitral or left ventricular hypoplasia is considered an uncorrectable cofactor.

The similar repair of the doubly commited ventricular septal defect, with creation of a left ventricular–subaortic tunnel, does not present a significant increase in operative risk; however, an increased incidence of the late development of discrete subaortic stenosis following repair has been reported.[94]

Double-Outlet Right Ventricle with Pulmonic Stenosis

The initial surgical series of DORV with pulmonary stenosis in association with a subaortic ventricular septal defect reported an overall mortality of 32% in 22 patients.[95] Exclusion of the first four patients in this series, however, resulted in an operative mortality of 16%. In a subsequent study, operative mortality was reduced to 11%, although late death from arrhythmia was frequent.[96] In the current decade, patients with DORV, subaortic ventricular septal defect, and pulmonary stenosis are managed in accordance with institutional protocols applied to tetralogy of Fallot.[97] When simple repair of the pulmonary obstruction appears feasible by angiography, intracardiac repair at 6 to 12 months of age is recommended. The risks of this repair do not appear different from those for repair of DORV with subaortic ventricular septal defect in the absence of pulmonic stenosis.[11] However, as this form of DORV is frequently accompanied by profound newborn cyanosis, severe dysplasia of the pulmonary arteries, or anomalies of the coronary arteries, initial palliative shunting is often required.[96,98] When complex repair to include a right-ventricle-to-pulmonary-artery homograft conduit is anticipated, preliminary palliative shunting is also indicated, with definitive repair delayed until four or five years of age.[99]

Double-Outlet Right Ventricle with Subpulmonary Ventricular Septal Defect

In general, surgical survival rates are lower in patients with DORV and a subpulmonary or noncommitted ventricular septal defect.[11] Historically, three surgical approaches to the Taussig–Bing type of DORV have been performed: 1) closure of the ventricular septal defect to tunnel the left ventricle output to the pulmonary artery, with subsequent atrial baffle procedure (Mustard or Senning); 2) a long interventricular tunnel to establish left-ventricle-to-aorta continuity, with direct or conduit continuity of the right ventricle to the pulmonary artery; and 3) left-ventricle-to-subpulmonary-outflow-tract tunnel, with an arterial translocation procedure (Jatene or Damus–Stansel–Kaye).

In most cases of DORV with subpulmonary ventricular septal defect, the defect is bordered superiorly by the pulmonary valve, and the ventricular septal defect can be repaired in a manner such that an unobstructed left ventricle–pulmonary artery connection is formed. In conjunction with an atrial baffle procedure, this type of repair of the Taussig–Bing heart was first reported in 1969.[100] However, the venous switch (Mustard or Senning) and ventricular septal defect closure in DORV have remained associated with a high operative and late mortality rate in most centers.[90,101] Because of these poor results, direct ventricular septal defect closure accompanied by arterial translocation for repair of the Taussig–Bing type of anatomy has become the preferred approach.[11,102–104] The principles of coronary transfer do not appear different from those applied in classic transposition.[101] Alternatively, recognition that the infundibular septum and ventriculoinfundibular fold are devoid of conduction tissue has allowed enlargement of the ventricular septal defect, with subsequent placement of a tunnel to establish left-ventricle-to-aorta continuity in a limited number of these patients.[105,106]

Regardless of the type of repair preferred, surgery should be attempted by three months of age, due to the rapid evolution of pulmonary vascular disease and myocardial hypertrophy. Increased patient numbers and longterm followup will be required to determine the procedure of choice in this type of anatomy. However, current data suggest superior results with the interventricular tunnel or arterial transfer as compared with a venous switch and ventricular septal defect closure (Fig. 72–17).

PATIENT STATUS FOLLOWING SURGICAL REPAIR OF DOUBLE-OUTLET RIGHT VENTRICLE

The heterogeneity of malformations that constitute DORV make analysis of the outcome of corrective surgery difficult. However, in the current decade, improved hemodynamic results have been reported in most forms of DORV, associated with a low operative mortality rate.[11,92,107]

Perioperative mortality following repair of DORV has been attributed to persistent low cardiac output, residual pulmonary hypertension, and hemorrhage. Recent clinical and hemodynamic followup suggests that most patients surviving repair of DORV in the current era are New York Heart Association Functional Class 1. Early primary repair of DORV, as opposed to initial palliation with subsequent repair, is no longer projected as a risk factor and may further improve surgical results.

Residual hemodynamic abnormalities, the potential need for reoperation, and late postoperative arrhythmias are primary considerations in the followup of these patients. A residual ventricular septal defect ($Qp/Qs > 1.5$) may occur in a significant number of patients, particularly following construction of a complex interventricular tunnel. Subpulmonic stenosis has been recognized, due

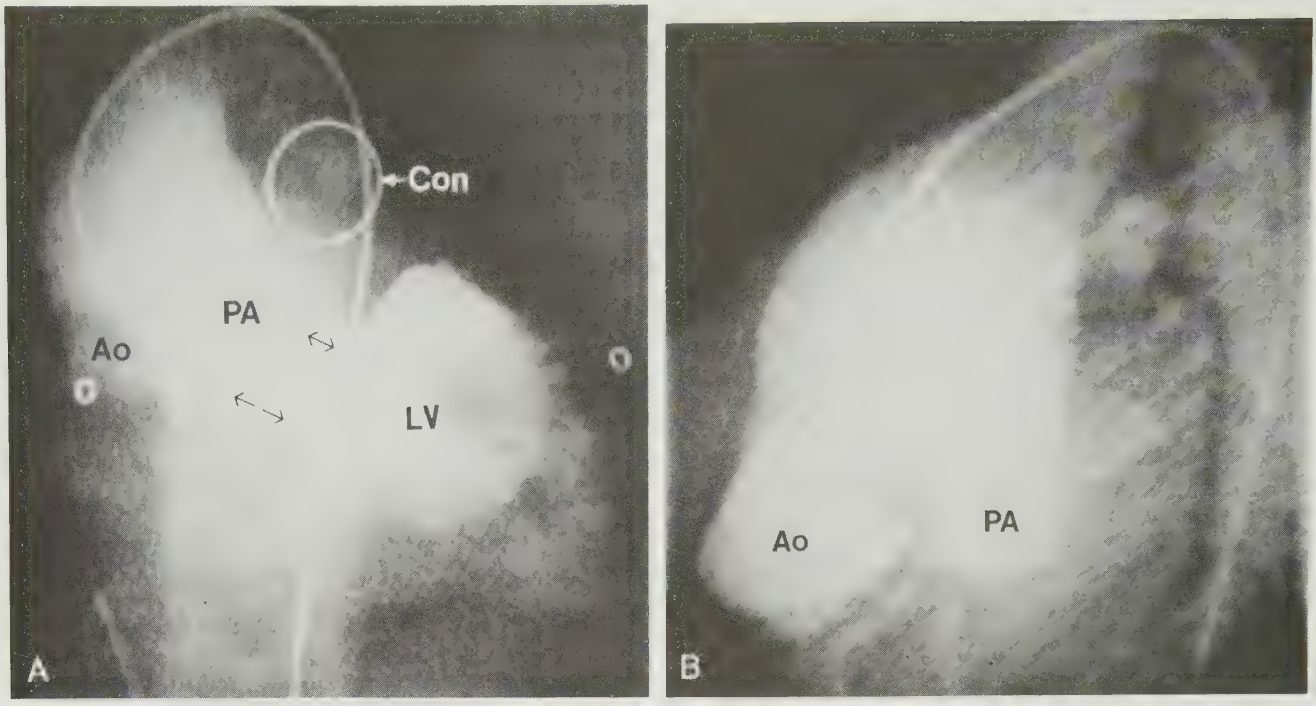

Fig. 72–17. Double-outlet right ventricle with subpulmonic ventricular septal defect, following correction with Kaye–Damus–Stansel procedure. A) Left ventriculogram (LV) demonstrating the subpulmonic conus (arrows), and filling of the proximal main pulmonary artery (PA) followed by opacification of the ascending aorta (Ao). The valved conduit (Con) establishing right ventricle–pulmonary artery continuity is evident. B) Lateral-view aortogram, emphasizing the anterior–posterior great artery relationship, and wide area of arterial anastomosis establishing the arterial repair, without associated coronary translocation.

either to muscular hypertrophy of the conus or tunnel compromise of the subpulmonic outflow tract, although not severe in degree. Less frequently, subaortic stenosis due to the baffle obstruction may produce a significant systolic ejection gradient requiring revision. As in other complex forms of congenital heart disease, ventricular dysfunction may evolve in association with longterm palliation.

Indications for reoperation are a function of multiple variables, both anatomic and hemodynamic. The reoperations for DORV have included replacement of an extracardiac conduit, repair of tunnel dehiscence or tunnel revision, closure of residual ventricular septal defects, and atrioventricular valve replacement.[11,107]

A disturbing prevalence of cardiac arrhythmias and sudden cardiac death following repair of DORV has been recognized, with late sudden death potentially exceeding the operative mortality.[96,108] Definitive repair at an older age and persistent elevation of pulmonary artery pressure have been identified as significant factors for this risk. However, other series have reported no significant postoperative dysrhythmias or sudden death following repair of DORV.[92,107] From our perspective, persistent atrial arrhythmias, ventricular ectopy, or syncope provide justification for postoperative electrophysiologic studies in this patient group. Given the anatomic and hemodynamic similarities to the repair of tetralogy of Fallot, or an arterial or venous switch procedure associated with ventricular septal defect closure, the indications for electrophysiologic study should not differ.[109]

DOUBLE-OUTLET LEFT VENTRICLE

Perhaps the rarest of ventriculoarterial connections, and at times the most controversial, double-outlet left ventricle (DOLV) has been reported in over 100 cases to date.[5] The unequivocal description of a case of DOLV with an intact ventricular septum in 1970 confirmed the existence of this anomaly,[110] which previously had been considered an embryologic improbability or impossibility.[111,112] Subsequent definition of "double-outlet ventricle" as the origin of one and 50% or more of the other great artery from the same ventricle has resulted in increased recognition of this anomaly.[4] As Bharati et al., have indicated, as more cases of DOLV are recognized, similar variations in great artery relationship and ventricular septal defect position will be described, analogous to DORV.[113]

In most cases of DOLV there is a hypoplastic or deficient infundibular septum, and poorly expanded subpulmonary conus. The successful surgical correction of this type of DOLV, which is similar to tetralogy of Fallot, was first reported in 1971.[114] Subsequently, multiple anatomic variations in association with DOLV have been described.

The diagnosis of DOLV should be considered cautiously when the presence of ventricular inversion (l-loop) in association with DORV has not been excluded. As of this writing, and in a recent review, no cases of DOLV have been documented by echocardiography.[115] Although extremely rare, DOLV may be associated with abnormalities of any aspect of cardiac anatomy, and a segmental approach to diagnosis is mandatory. Palliative or corrective surgery is usually feasible, following accurate anatomic definition.

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CHAPTER 73

Ventricular Inversion

Charles E Mullins

DEFINITION

Ventricular inversion in combination with transposition of the great arteries is referred to as L-transposition,[1] "corrected transposition,"[2] "physiologically or congenitally[3] corrected transposition," or "atrioventricular discordance with transposition."[4] Ventricular inversion alone is defined simply as atrioventricular discordance.[4] Specifically, the *morphologic* right atrium is connected to the *morphologic* left ventricle, and/or the *morphologic* left atrium is connected to the *morphologic* right ventricle (Fig. 73–1). In this chapter, all subsequent references to *right* and *left* in relation to chambers will refer only to the *anatomic structure* or *morphology* of the chamber without regard to the spatial relationships, the connections to other chambers or vessels, or the physiologic function of the chamber. This use of the adjectives is analogous to the use, for example, with the right or left hand. The hands were named according to the side of the body to which they were attached, however, regardless of where the hand is or what task it is performing (e.g., over the head, behind the back or even totally disconnected from the body), the hand morphologically remains a right or left hand and one does not refer to the "morphologic" or "anatomic" right or left hand. As long as one uses only morphology to define the chambers, this analogy holds true for the cardiac chambers and no redundant adjectives such as anatomic, structural, or morphologic right or left will be used in this chapter.

Each of the four cardiac chambers has distinct identifying features independent of their spatial location or cardiac connections. The right ventricle is identified by its coarse apical trabeculations and by the muscular conus separating the inflow or sinus portion from the infundibular portion of the ventricle.[5] The tricuspid valve, a right ventricular structure, has characteristic multiple papillary muscle attachments to the ventricular septum and is separated from the semilunar outflow valve by the conus. The left ventricle has much finer apical and septal trabeculations, and has no outflow conus or infundibulum.[5] The atrioventricular mitral valve, which is structurally part of the left ventricle, has a direct fibrous attachment to the outflow semilunar valve of the left ventricle. The anterior leaflet of the mitral valve actually forms one side of the outflow tract of the left ventricle. The mitral valve usually has two distinct papillary muscles and no septal attachments.

The right atrium is best identified angiographically and anatomically by the very broad base and blunt configuration of the right atrial appendage as well as the extension of the pectinate muscles from the appendage into the right atrium.[5] This is in contrast to the left atrium with its usually narrow-based, longer, and finger-like left atrial appendage with no pectinate muscular extension into the left atrium.[5] When the systemic veins follow their usual course, they usually enter the right atrium and help to identify the right atrium although this is not a reliable determinant because of known anomalous systemic venous connections. The same holds true for the left atrium and the pulmonary veins.

Ventricular inversion can be an isolated anatomic defect and, as such, is not necessarily associated with any other structural defect. However, ventricular inversion usually is found in association with other cardiac defects as the major embryologic and structural abnormality in a variety of complex lesions. Ventricular inversion is usually, but not necessarily, associated with transposition of the great arteries. In this common association with

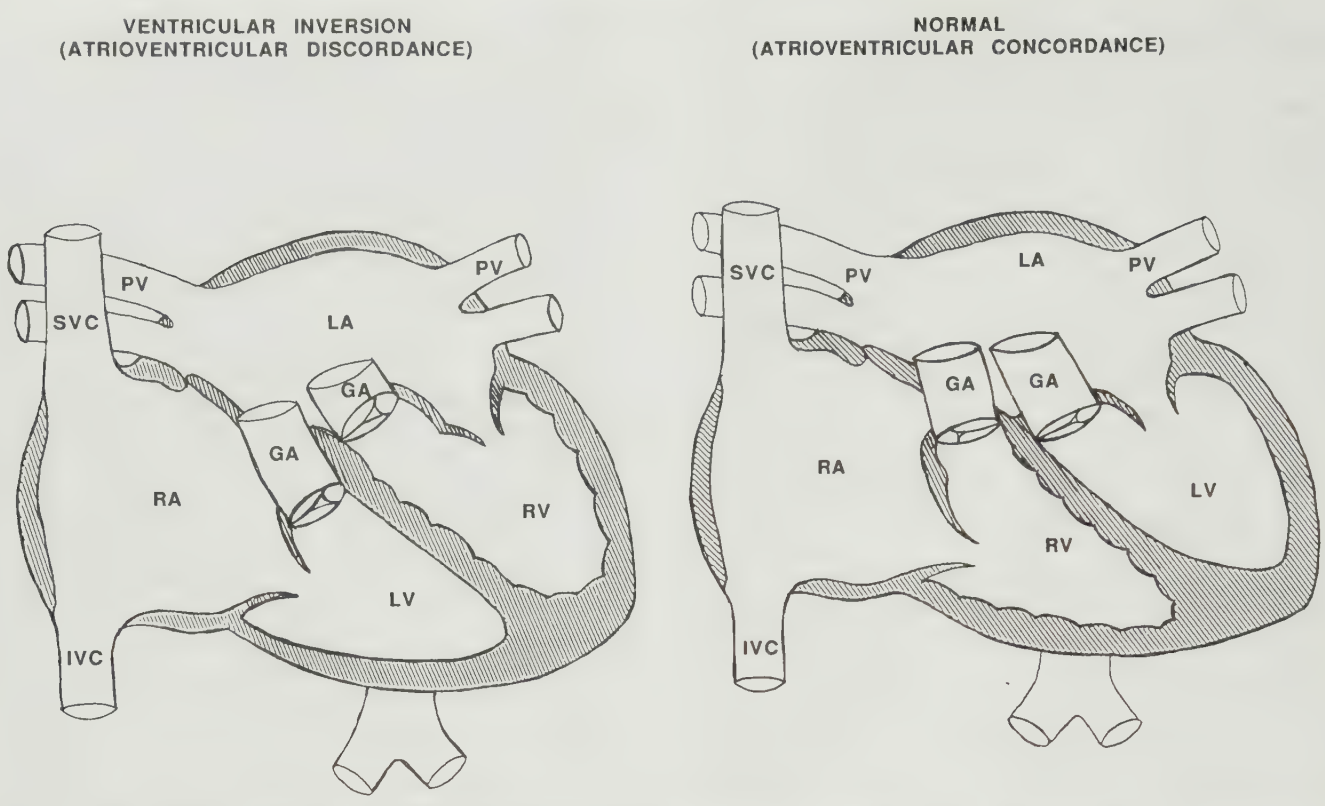

Fig. 73–1. Line diagrams of ventricular inversion–atrioventricular discordance (left diagram) compared to a diagram of normal atrioventricular connection–atrioventricular concordance (right diagram). In ventricular inversion, the right atrium connects to the smooth-walled left ventricle. There is direct fibrous continuity between the right atrioventricular valve and the right semilunar valve (absence of a conus). In ventricular inversion, the left atrium connects to the trabeculated (scalloped inner wall) right ventricle. The right ventricle has a muscular mass (conus) separating the left atrioventricular valve and the left semilunar valve. This compares to the normal (right diagram) where the right atrium connects to the right ventricle and the left atrium connects to the left ventricle.

transposition of the great arteries, the terminology L-transposition or corrected transposition refers respectively to the commonly occurring spatial relationships of the two great arteries with this combination, or to the physiologically corrected status of the combined lesions. Because of the much higher incidence of ventricular inversion in association with transposition, the majority of this chapter will be on the discussion of ventricular inversion with transposition of the great arteries.

INCIDENCE

Ventricular inversion with two well-defined ventricles, even with the commonly associated transposition of the great arteries and other associated lesions such as ventricular septal defect and pulmonary stenosis, is a relatively rare lesion accounting for only about 0.5% of clinically apparent congenital heart disease.[6,7] Of this total group of patients with ventricular inversion and transposition of the great arteries, probably fewer than 1% have no other associated abnormalities.[8–10] Isolated ventricular inversion with normally connected great arteries (i.e., without transposition) occurs in fewer than 1% of all cases of ventricular inversion. In addition to those cases of ventricular inversion with two well-defined ventricles, as many as 75% of all cases of univentricular hearts (as described in Chapter 74) embryologically are varieties of ventricular inversion. Because of their unique anatomy and different hemodynamic problems, univentricular hearts usually are not included under the discussions or tabulations of ventricular inversion.

EMBRYOLOGY: L-LOOPING

The normal heart with normal atrioventricular relationships is a result of so-called Dextro or D-looping of the embryonic heart tube.[11] The development of ventricular inversion or atrioventricular discordance and the resultant anatomy is explained by the embryologic phenomena or Levo or L-looping of the embryonic heart tube[12] as opposed to this normal D-looping. Knowledge of this embryology helps in the understanding of ventricular inversion and the associated lesions.

The embryonic heart is formed from primitive blood islands into a relatively straight and undifferentiated tube at approximately 20 days' gestation.[11,13] Within the same day of gestation, the segments of the tube differentiate into the primitive aortic arches, the bulbus cordis, the primitive ventricle, the sinus venosus, and the venous channels. The bulbus cordis will develop into the truncus and the right ventricle whereas the primitive ventricle becomes the early left ventricle. The primitive ventricle separates from the venous confluence by primordial atrioventricular valve tissue. Shortly after the differentiation within the cardiac tube, at about 23 days' gestation, the blood flow in the venous channels begins

to lateralize, normally with the systemic veins lateralizing to the right side of the embryo into the primitive right atrium. At almost the same time, the center of the tube begins to fold on itself and rotate anteriorly, normally to the right of the embryo, D-looping (Fig. 73–2). This brings the primitive right ventricle in a front-to-back apposition to the rightward lateralized systemic veins and side by side to the primitive left ventricle. Simultaneously, the left-sided venous chamber is producing an outpouching dorsally and on the left that will contact and connect with the pulmonary venous buds arising from the lungs. Also, the atrioventricular valve is migrating to the right within the embryonic heart to straddle the inflow of both the right and left ventricles. This produces situs solitus of the atria with the normal D-looping; the right or systemic venous atrium is in apposition to and drains into the right ventricle. The eventual left or pulmonary venous atrium with the attached pulmonary veins remains connected to the left ventricle (Fig. 73–3) (i.e., atrioventricular concordance with situs solitus of the atria).

With isolated L-looping of the heart tube, the heart tube folds to the left while all of the other lateralization remains the same (situs solitus of the atria)[12] (Fig. 73–4). The right ventricle comes in apposition to the left or pulmonary venous atrium, and the left ventricle remains in apposition to, and connected to, the right or systemic venous atrium (Fig. 73–5) with resultant atrioventricular discordance or ventricular inversion with situs solitus of the atria.

If the early cardiac venous structures had lateralized to the left so that the systemic veins were on the left of the embryo, the L-loop would have resulted in the proper or concordant atrioventricular relationships (nonventricular inversion) but with situs inversus of the atria. Similarly, with the left-sided lateralization (situs inversus) of atria, the D-looping of the heart tube would

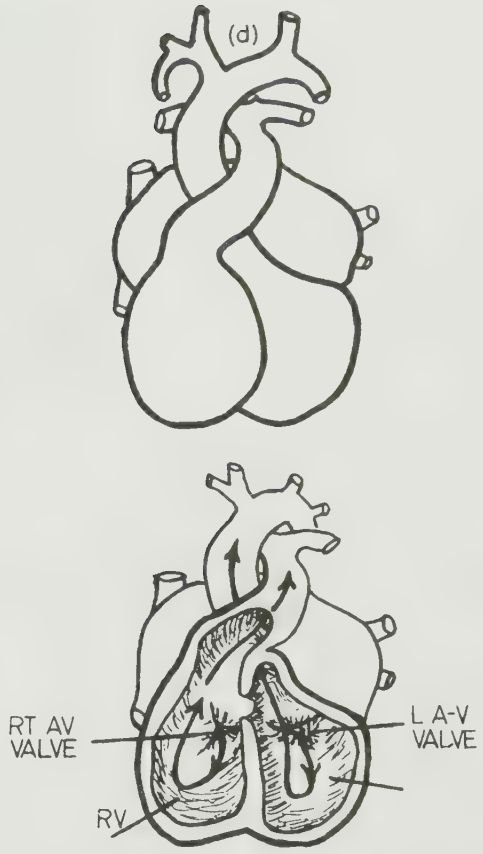

Fig. 73–3. Later stage D-looping of the heart tubes. Upper diagram shows intact heart; lower diagram shows cutaway of the same stage embryologically. The right ventricle now is in apposition to the right-sided systemic veins and right atrium whereas the left ventricle is in apposition to the left atrium and the pulmonary venous system (i.e., atrioventricular concordance).

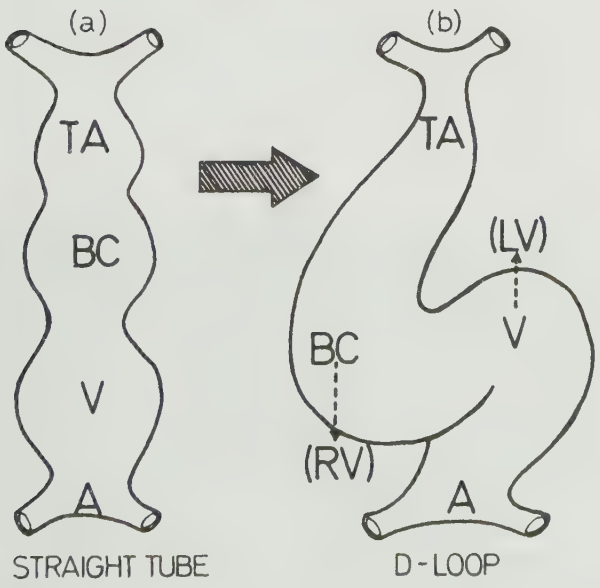

Fig. 73–2. Normal D-looping of the primitive cardiac tube. The bulbus cordis (primitive right ventricle) moves ventrally and to the right in the body, leaving the primitive ventricle (primitive left ventricle) dorsally and to the left in the body.

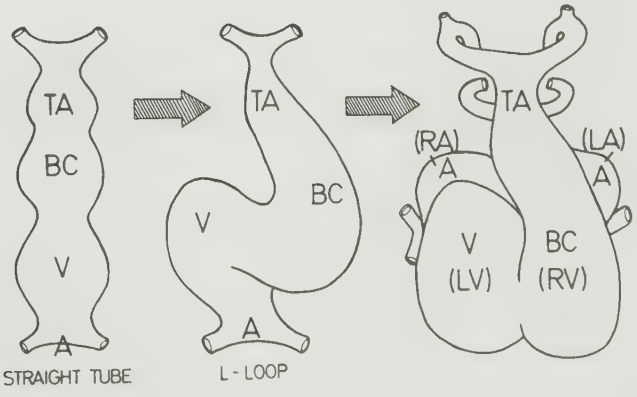

Fig. 73–4. L-looping of the primitive cardiac tube moving the bulbus cordis (primitive *right* ventricle) ventrally and to the left in the body leaving the primitive ventricle (primitive left ventricle) dorsally and to the right in the body.

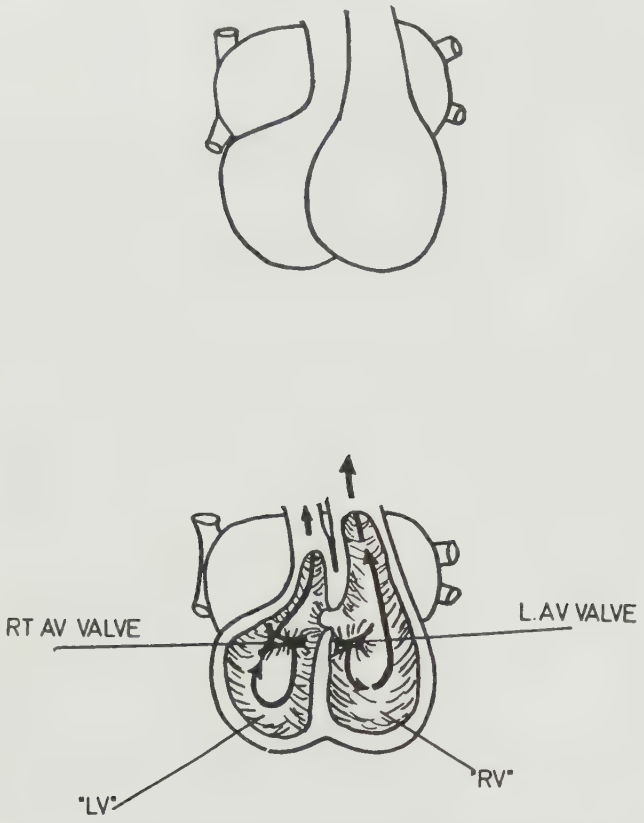

Fig. 73–5. Late stage L-looping of the heart tube. The intact heart (top) and cutaway of the same stage (bottom). The right ventricle, now on the left in the body, is in apposition to the left atrium and pulmonary veins whereas the left ventricle, now on the right in the body, is in apposition to the right atrium and systemic venous system–atrioventricular discordance or ventricular inversion.

result in atrioventricular discordance (ventricular inversion with situs inversus). The embryologic aspects of situs and looping are discussed further in Chapter 75.

The embryology of the great artery relationships and eventual connections is still poorly understood. Usually there is little discussion or at most superficial reference to this important event in the development of the final heart. The truncus is similar to the sinus venosus in that both are originally mesenchymal structures and early in development more associated with the vessels leaving and entering the heart tube respectively than to the heart itself. There is agreement that the truncus divides into the aortic and pulmonary arteries by the ingrowth of mesenchymal ridges and that these ridges, which become the aortopulmonary septum, fuse with the endocardial outlet septum.[14] There is no knowledge or agreement on how this occurs. In the normal heart with normal atrioventricular, or D-loop, embryology and the usual ventriculo–arterial connections, this requires a 180° rotation of the aortopulmonary septum. In transposed great arteries, this rotation does not occur. In ventricular inversion, or L-loop embryology of the heart tube, it seems normal for the rotation of the aortopulmonary septum *not* to occur as though the rotation were more influenced by the looping of the heart tube than by the eventual internal structures of the heart.

ASSOCIATED LESIONS

Normally Connected Great Arteries

Isolated ventricular inversion (atrioventricular discordance), without associated transposition of the great arteries—pulmonary artery arises from the right ventricle (Fig. 73–6) and the aorta from the left ventricle (Fig. 73–7) with ventriculo–arterial concordance—is the rarest "defect" linked with ventricular inversion.[15] It results in the most severe hemodynamic abnormality of any associated defect. The net physiologic effect is the same as that of transposition of the great arteries in association with atrioventricular concordance (nonventricular inversion). Without more associated intracardiac shunt lesions, ventricular inversion with normally connected great arteries results in severe cyanosis and is life-threatening.

The combination of ventricular inversion (atrioventricular discordance) with normally connected great arteries (ventriculo–arterial concordance) also occurs in association with situs inversus of the atria. Thus, the patient has situs inversus of atria, ventricular inversion (atrioventricular discordance) as a result of D-looping, and normally connected great arteries (ventriculo–arterial concordance) (i.e., right atrium to left ventricle to aorta). The patient still has transposition physiology.

Transposition of the Great Arteries

Most cases of ventricular inversion occur with transposition of the great arteries (ventriculo-arterial discordance). In this combination, the right ventricle remains very muscular, becomes more spherical, receives pulmonary venous blood, and pumps to the systemic circulation (Fig. 73–8). The left ventricle, on the other hand, is less muscular, becomes somewhat flattened and wraps partially around the right ventricle, receives systemic venous blood, and pumps to the pulmonary circulation (Fig. 73–9). The resultant circulation is corrected physiologically, and in the absence of other defects can function normally, leading to the synonym of embryologically corrected transposition of the great arteries. However, only 1% of cases of ventricular inversion with transposition of the great arteries do not have other significant associated defects.[16,17]

Ventricular Septal Defect

Next to transposition of the great arteries, the most commonly associated defect with ventricular inversion is a ventricular septal defect. This occurs in approximately 80% of the cases.[18] Any type or location of ventricular septal defects may occur, or multiple types may appear together. The net hemodynamic effect of the ventricular septal defects in patients with ventricular inversion and transposition of the great arteries is identical to that in patients with ventricular septal defects in otherwise normal hearts; it results in shunting from the systemic to the pulmonary circulation. In the patient with ventricular inversion, however, this is shunting from the right ventricle into the left ventricle. Like the ventricular septal defect in patients with otherwise normal hearts, the degree of hemodynamic alteration in these patients is related to a combination of factors, including the size of the ventricular septal defect, the total pulmonary resistance, and the degree of any associated pulmonic stenosis. The majority of patients with ventricular inversion and large ventricular septal defects have associated pulmonic stenosis. As a consequence, very few patients with ven-

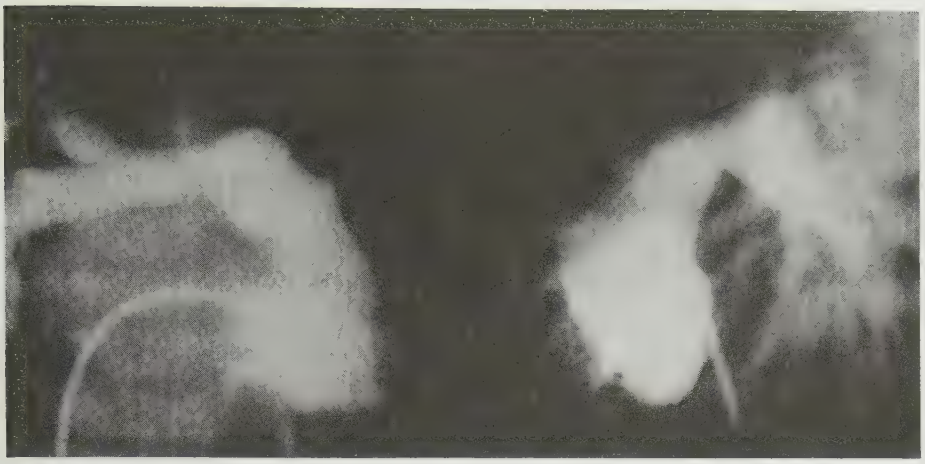

Fig. 73–6. Ventricular inversion with normally connected great arteries and atrioventricular discordance with ventriculo–arterial concordance. Posteroanterior (left) and lateral (right) right ventricular angiocardiograms. The leftward and posteriorly displaced trabeculated right ventricle gives rise to the pulmonary artery. This ventricle is connected to the left atrium and receives fully saturated pulmonary venous blood.

tricular inversion, transposition of the great arteries, and two distinct ventricles develop problems of congestive failure because of the ventricular septal defect. In the absence of any associated pulmonic stenosis, infants with this combination will develop congestive heart failure and/or pulmonary vascular disease similar to conditions in infants who have an isolated large ventricular septal defect in an otherwise normal heart.

Pulmonary Stenosis

Pulmonary stenosis, another commonly associated lesion with ventricular inversion and transposition of the great arteries, usually coexists with the ventricular septal defects. Some degree of pulmonary stenosis occurs in at least 50% of cases, and half of these are significant.[17,19] The pulmonary stenosis is usually subvalvular and results from a bulging of the malaligned ventricular septum and/or actual membranous subvalve excrescences. There are cases of aneurysms of the membranous ventricular septum bulging from the systemic right ventricle into the subpulmonic left ventricular outflow tract causing subpulmonic obstruction.[20] In a few cases, there is actual valve pulmonary stenosis with bicuspid, or even unicuspid, valves. Significant pulmonary stenosis in association with a ventricular septal defect in these patients can result in a "tetralogy" type of hemodynamics with the development of shunting of desaturated blood from the left ventricle into the systemic circulation.

Atrioventricular Valve Abnormalities

Structural abnormalities of the tricuspid valve occur in at least 90% of all patients with ventricular inversion.[18] These abnormalities can be minor, including elongation of the leaflets, or major, such as an Ebstein's type malformation with various degrees of displacement of the valve into the right ventricle.[21] Of the structurally abnormal valves, approximately 30% are functionally abnormal during infancy and childhood. In general, the functional abnormality of the tricuspid valve progresses in individual patients with age, as does the overall incidence of the functional valve abnormalities in patients with ventricular inversion and transposition of the great arteries. When the valve is abnormal functionally, it usually is insufficient; this systemic atrioventricular valve regurgitation often is the major hemodynamic abnormality.

In addition to the specific abnormality of the tricuspid valve, straddling of the ventricular septum of either of the atrioventricular valves can occur with an inlet ventricular septal defect. These valve abnormalities may not have significant or recognizable hemodynamic consequences by themselves and can go undetected. On the other hand, straddling atrioventricular valves may complicate, if not prohibit, eventual corrective surgical procedures.

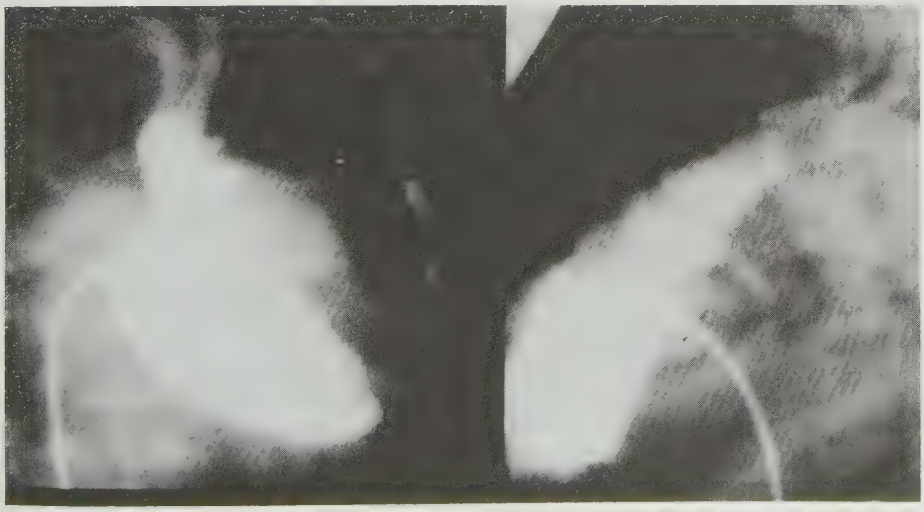

Fig. 73–7. Ventricular inversion with normally connected great arteries and atrioventricular discordance with ventriculo–arterial concordance. Posteroanterior (left) and lateral (right) left ventricular angiocardiograms. The rightward (in the chest) and anteriorly displaced smoother-walled left ventricle gives rise to the aorta (there is some filling of the pulmonary artery through a ventricular septal defect). This left ventricle is connected to the right atrium and receives systemic venous blood (same patient as shown in Fig. 73–6).

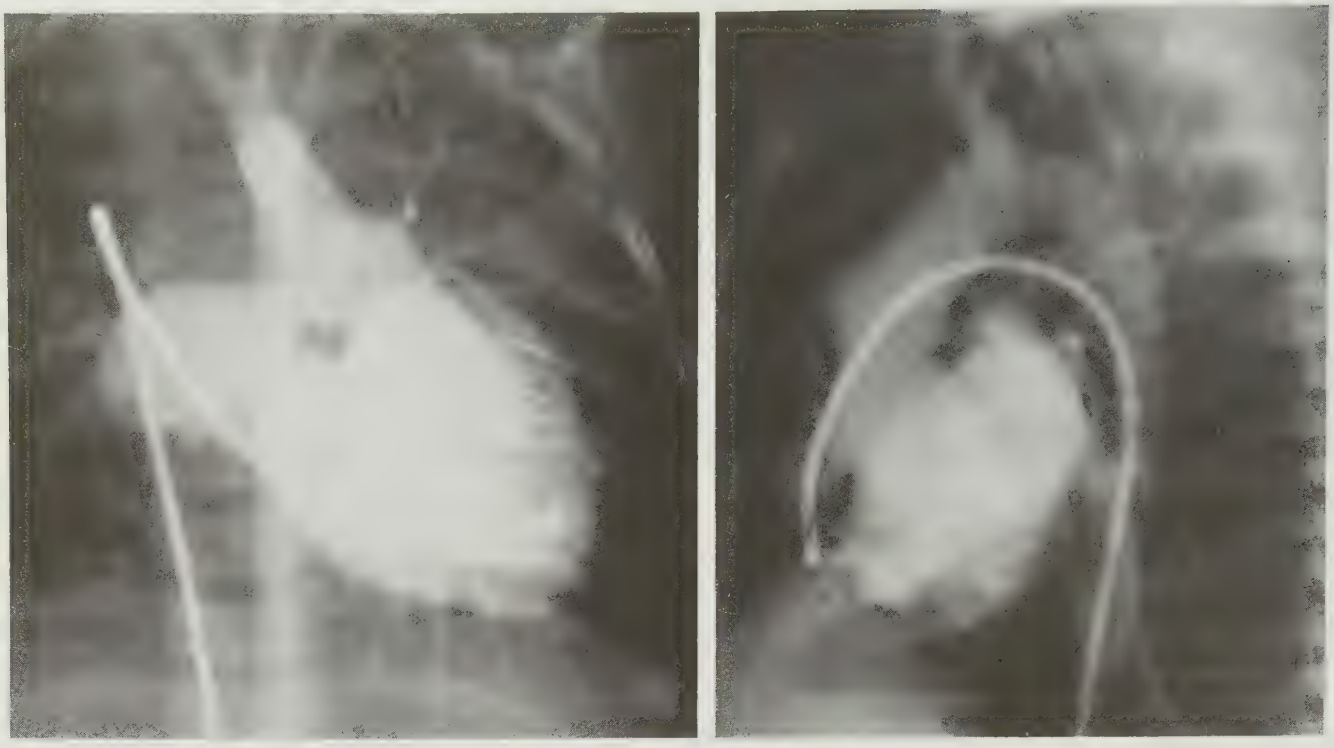

Fig. 73–8. Ventricular inversion with transposition of the great arteries and atrioventricular discordance with ventriculo–arterial discordance. Posteroanterior (left) and lateral (right) angiocardiograms. Recirculation from the lungs shows the left atrium emptying into the right ventricle, which is heavily trabeculated, has a distinct conus, and empties into the aorta.

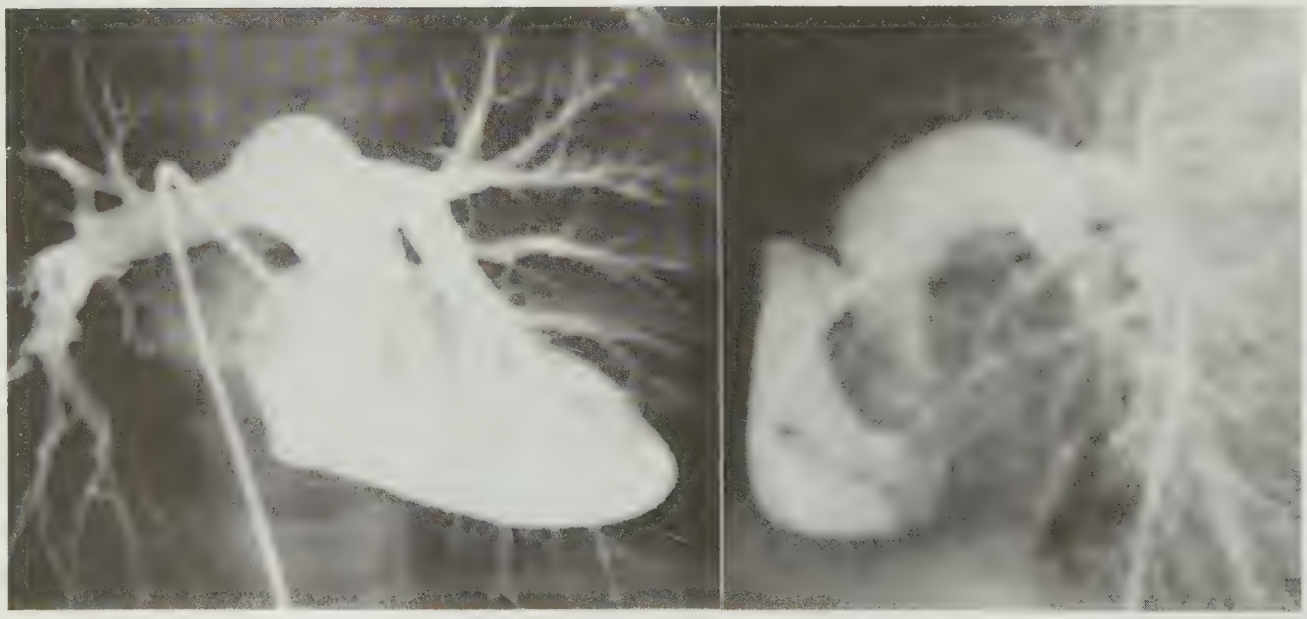

Fig. 73–9. Ventricular inversion with transposition of the great arteries and atrioventricular discordance with ventriculo–arterial discordance. Posteroanterior (left) and lateral (right) angiocardiograms in the smooth-walled, pear-shaped left ventricle which empties into the pulmonary artery. The catheter passage and blood flow are from the right atrium into the left ventricle (same patient as shown in Fig. 73–8).

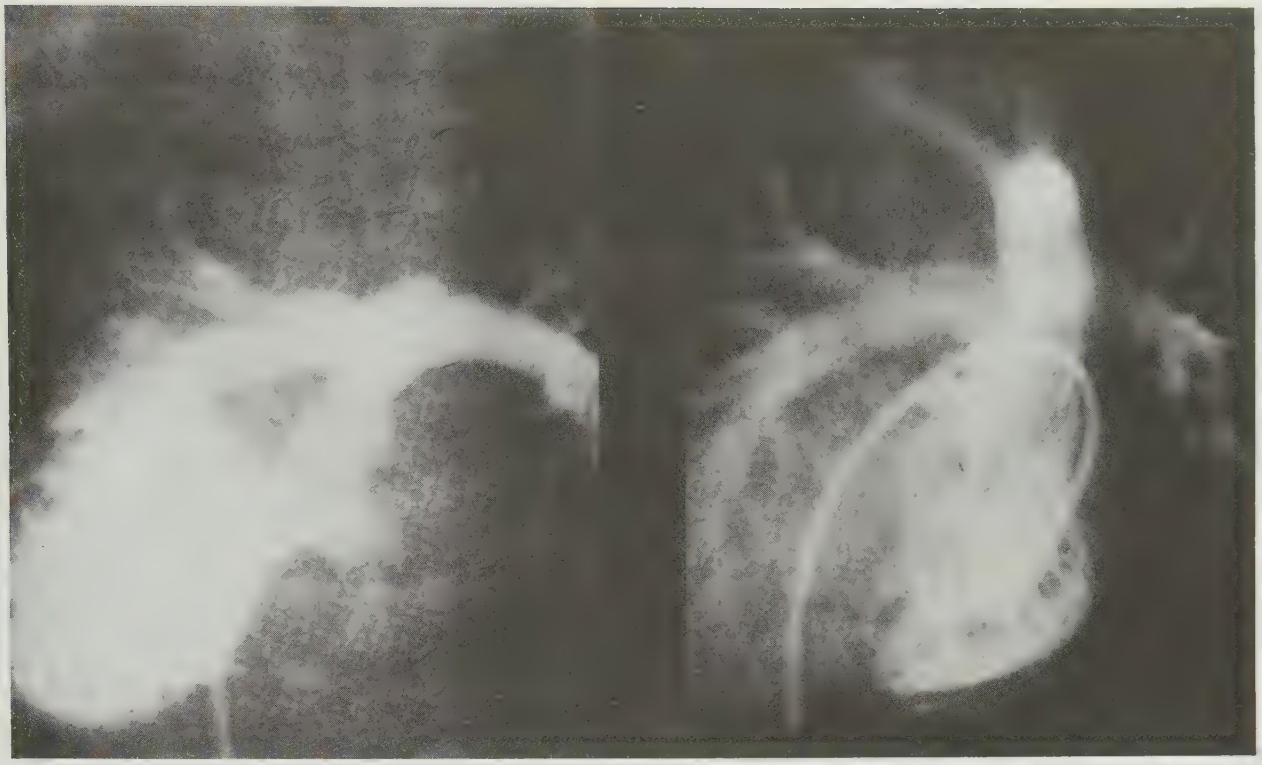

Fig. 73–10. Ventricular inversion, transposition of great arteries, ventricular septal defect, and pulmonary stenosis with dextrocardia and situs solitus of the atria. Posteroanterior angiocardiograms in the left ventricle (left panel) and in the right ventricle (right panel). The left ventricular angiocardiogram cuts the ventricular septum on edge and shows the ventricular septal defect.

Conduction Abnormalities

Because of the atrial to ventricular septal malalignment and the position of the pulmonary valve, the normal AV node does not give rise to a normal AV conduction bundle.[22] Instead, an additional or accessory AV node exists that gives rise to an abnormally positioned atrioventricular conduction bundle. This abnormal bundle penetrates more anteriorly and runs superficially down the anterior septal surface of the left ventricle and pulmonary outflow tract. In the presence of a perimembranous ventricular septal defect, the bundle runs anterior to the defect, or, in the case of less malaligned atrioventricular relations, both the normal and the accessory bundles penetrate into the ventricular septum and straddle the top and bottom of the left ventricular side of the ventricular septal defect. As a result of this precariously positioned AV bundle, naturally occurring AV conduction abnormalities and surgical AV block are common in patients with ventricular inversion. Approximately 10% of these patients present initially with complete AV block.[23] Another 20 to 30% will have first-degree or second-degree AV block initially. This has the tendency to progress to complete AV heart block as patients age.[24] The incidence of complete AV block in older children and adults is as high as 30%. The complete AV block may occur spontaneously even in the absence of earlier lesser degrees of AV block. AV block in patients with ventricular inversion also has been precipitated by anesthesia, cardiac catheterization, or even the thoracotomy prior to any actual cardiac surgery. Because of the associated defects usually present, complete AV block may not be well tolerated; usually, pacemaker therapy is recommended early after the recognition of complete AV block.

Dextrocardia

Dextrocardia with situs solitus (or mesocardia with situs solitus) occurs in approximately 25% of patients with ventricular inversion and transposition of the great arteries.[7,24] The high incidence of this easily detected, frequently associated defect actually should suggest the major underlying ventricular inversion with transposition. This abnormality does not complicate the hemodynamics, however, and may complicate understanding of the hemodynamics. The dextrocardia presumably results from the rightward rotation of the cardiac mass from its embryonic post-L-loop levoposition (opposite to the leftward rotation of the D-loop heart) as it descends into a more thoracic location. During echocardiographic or angiocardiographic evaluation of these patients, the dextrocardia and its effect on the position of the ventricular septum must be recognized. In most patients with this combination and the dextrocardia, the septum lies in a straight anterior/posterior plane and thus is best cut on edge by a straight anterior–posterior projection.

Dextrocardia with situs solitus also will compromise any surgical approach to intracardiac lesions. The rotation of the ventricular mass in front of the right atrium will hinder normal cannulation of the venae cavae and may interfere with a right atrial approach to such structures as the ventricular septal defect.

In addition to dextrocardia, positional abnormalities of the chambers due to peculiarities in rotation during development are

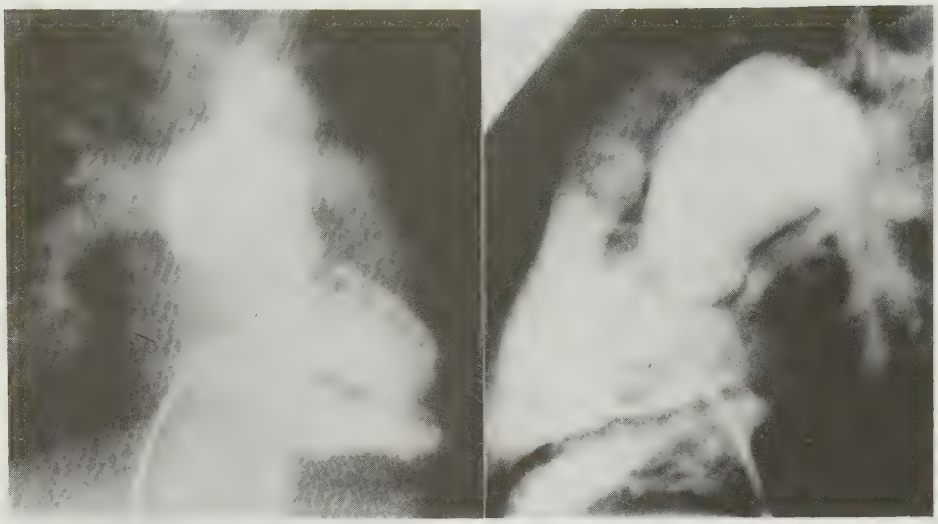

Fig. 73–11. Ventricular inversion, transposition of the great arteries, ventricular septal defect, and pulmonary stenosis with associated cephalocaudal (''upstairs-downstairs'') relationship of the ventricle. Posteroanterior (left) and lateral (right) angiocardiogram in the more cephalad right ventricle fills the aorta but also, through the ventricular septal defect, the left ventricle and pulmonary artery.

common with ventricular inversion and transposition of the great arteries. Because of the relative positions of the ventricles to each other, these abnormally positioned hearts are sometimes referred to as ''upstairs-downstairs'' hearts or, because of the resultant twisted pathways of the atrioventricular connections, they are called ''crisscross'' hearts (Figs. 73–11 and 73–12). Although these terms help to identify the relative positions of the chambers, they do not clarify the exact anatomy and physiology. Since these positional abnormalities may occur with normal atrioventricular and ventriculo–arterial connections, the positional terminology must be used only in conjunction with the precise definition of the more important atrioventricular and ventriculoarterial connections and not as total diagnoses.

Rudimentary Ventricular Chamber

At least 75% of univentricular hearts with a double inlet left ventricle are ventricular inversions with transposition of the great arteries. These hearts usually are not included in the discussion of ventricular inversion but are in the large category of univentricular hearts. The basic embryology of a double inlet left ventricle is that of L-looping of the cardiac tube; in addition, these hearts have underdevelopment of the bulbus cordis into a right ventricle and along with this, an absent or incomplete migration of the atrioventricular valve toward the right ventricle. As a result, the sinus portion of the right ventricle is absent or markedly underdeveloped, and both atrioventricular valves empty into the left ventricle. With partial development of the right ventricle and partial migration of the valve, there will be straddling of the tricuspid valve. The one constant relationship in these hearts is that the right atrium empties into the left ventricle, thus meeting the criteria for atrioventricular discordance or ventricular inversion. As the name implies, these lesions represent types of single ventricle or univentricular heart and are included in Chapter 74.

Coronary Arteries in Ventricular Inversion and Transposition of the Great Arteries

The coronary arteries have the usual ''right'' and ''left'' morphology and follow a distribution appropriate for the *ventricles* arising from the aortic valve sinuses adjacent to the appropriate ventricle. The morphologic left coronary artery arises from a right-sided/posterior sinus and courses anteriorly and rightward over the left ventricle and anterior to the pulmonary valve ring, giving rise to the anterior descending and circumflex branches. The anterior descending artery courses further anteriorly in the interventricular

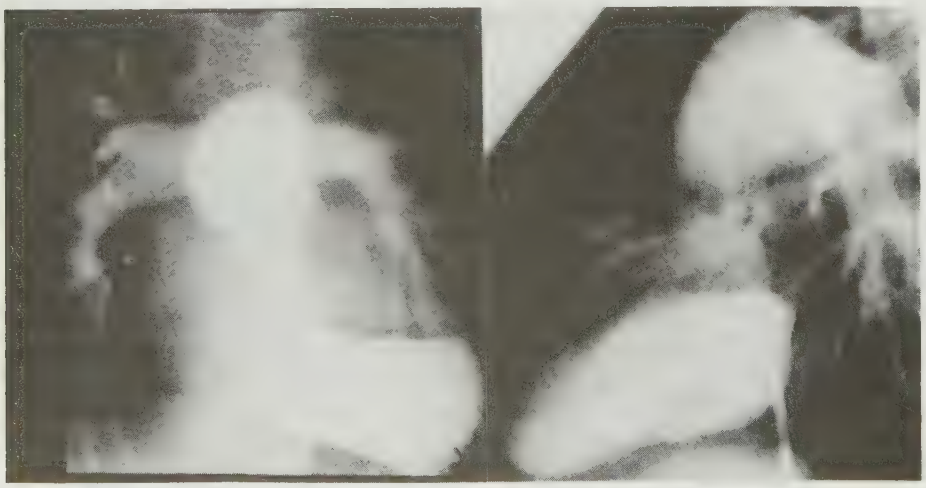

Fig. 73–12. Ventricular inversion, transposition of the great arteries, ventricular septal defect, and pulmonary stenosis with associated cephalocaudal (''upstairs-downstairs'') relationship of the ventricles (same patient as shown in Fig. 73–11). Posteroanterior (left) and lateral (right) angiocardiogram in the smoother-walled more caudal left ventricle fills predominantly the pulmonary artery.

groove, whereas the circumflex artery passes posteriorly and rightward around the atrioventricular groove of the mitral valve. The morphologic right coronary artery arises from a left-sided/posterior sinus and runs posteriorly over the right ventricle in the atrioventricular groove of the tricuspid valve to become the posterior descending artery. The most common coronary abnormality is a single coronary artery that arises from the right-sided/posterior sinus.[25,26] By itself, the coronary artery anatomy in ventricular inversion does not result in any functional abnormality but may complicate surgical approaches to associated defects with this lesion. The course of the left anterior descending coronary artery crosses over the anterior surface of the left ventricular outflow tract and represents an additional deterrent to a direct surgical approach to left ventricular outflow tract obstruction or a left ventricular approach to a ventricular septal defect.

HEMODYNAMICS AND PHYSIOLOGY

The hemodynamics and physiology of ventricular inversion depend entirely on the associated defects. When associated with transposition of the great arteries and no other abnormalities, ventricular inversion presents a truly ''corrected'' physiologic situation. The systemic venous blood returns to the right atrium, from there goes through the mitral valve into the left ventricle and then passes out into the pulmonary artery. After passing through the lungs, the pulmonary venous blood enters the left atrium. From the left atrium, the pulmonary venous blood passes through the tricuspid valve and into the right ventricle and from there into the aorta. With no associated shunts or obstruction, the pressures and saturations in the appropriate physiologic chambers and great vessels will be normal.[27]

Since most of the patients have associated ventricular septal defects with or without pulmonary stenosis, these lesions cause the major hemodynamic abnormalities. The effect of the ventricular septal defect will be a left-to-right shunt from the systemic to the pulmonary circulation. Although the ventricular septal defect is commonly associated with ventricular inversion and transposition, these patients rarely require early surgical intervention because of pulmonary overcirculation. In most cases, this is because of the associated pulmonary stenosis which, although seldom severe, is usually sufficient to ''protect'' the pulmonary vessels from overcirculation. The net physiologic effect of pulmonary stenosis with the ventricular septal defect in patients with ventricular inversion and transposition of the great arteries depends on the relative severity of the pulmonary stenosis and ventricular septal defect. In most cases, these two associated lesions achieve a relatively balanced situation with neither pulmonary overcirculation from too little pulmonary stenosis nor marked cyanosis from a severe pulmonary stenosis. The other interesting phenomenon with this combination of lesions (which is hemodynamically similar to tetralogy of Fallot) is that unlike the patient with tetralogy, the pulmonary stenosis in ventricular inversion, transposition and ventricular septal defect does not seem to progress to cyanosis but remains in the hemodynamic balance allowing nearly normal pulmonary flow.

The presence of tricuspid (left atrioventricular) valve incompetence often represents a more urgent and more progressive lesion.[10,28] The effect on the right ventricle's capability to function as a systemic ventricle is compromised more by this insufficiency than is a normal left ventricle with mitral valve regurgitation in an otherwise normal heart.

The presence of, or development of, complete atrioventricular block may be tolerated in the absence of other associated lesions or even in the presence of a balanced combination of ventricular septal defect with pulmonary stenosis. However, this tolerance appears less than in an otherwise normal heart; often, the moderately low ventricular rate will necessitate in a pacemaker.

Rarely a patient with isolated ventricular inversion (atrioventricular discordance) and normally connected great arteries (ventriculo–arterial concordance) presents hemodynamically exactly as the infant with noninverted ventricles (atrioventricular concordance) and associated transposition of the great arteries (ventriculo–arterial discordance).[29] These infants with isolated ventricular inversion are markedly cyanotic and like their counterparts, their degree of cyanosis and likelihood of survival depend upon the associated lesions.

CLINICAL FEATURES

The clinical features of ventricular inversion depend almost entirely on the associated defects.[6,30]

History

The extremely rare patient with isolated ventricular inversion and normally connected great arteries presents very early with marked cyanosis and acidosis. With an associated ventricular septal defect or other areas for mixing, the presentation may be slightly later, with more congestive heart failure and less cyanosis.

The patient with ventricular inversion with transposition of the great arteries and no other associated defects may not actually present to a cardiologist but rather be discovered as an adult on a routine physical examination or because of an abnormal chest roentgenogram. Occasionally, these patients, at any age, are detected because of a slow heart rate due to complete atrioventricular block.

In the large majority of patients with ventricular inversion and transposition of the great arteries and associated defects, the patients will present as young infants with a heart murmur and/or evidence of congestive heart failure. The rare infant with severe pulmonary stenosis and associated ventricular septal defect will present with cyanosis.[31,32]

Physical Examination

As with the hemodynamics and history, the physical examination depends predominately on the associated defects.[33] Unless there is associated severe pulmonary stenosis, most of these patients will be acyanotic. Even with ventricular septal defects or ventricular septal defects with pulmonary stenosis, there may be little or no distress. The one finding characteristic of ventricular inversion with transposition of the great arteries is the presence of a very loud, even palpable, single, second heart sound along the upper left sternal border.[33–35] This finding would otherwise suggest transposition in a cyanotic patient or very severe pulmonary hypertension in an acyanotic patient. Any murmurs and/or associated thrills on physical examination result from the associated lesion and usually are characteristic of the hemodynamically dominant associated lesion (i.e., ventricular septal defect, pulmonary stenosis, or tricuspid valve insufficiency).

Chest Roentgenogram

The roentgenogram, as with the other clinical findings, reflects not only the ventricular inversion with transposition but the associated defects. Characteristically, in patients with ventricular inversion and transposition of the great arteries, the upper left heart border is straightened corresponding to the leftward displacement of the ascending aorta.[36,37] In the absence of other significant defects or with the balanced ventricular septal defect and pulmonary stenosis, the heart size is normal as are the pulmonary vascular markings.[38] The presence of mesocardia or, in particular, dextrocardia with a straightened upper left heart border should suggest ventricular inversion with transposition.[39,40] In the presence of a large systemic to pulmonary shunt due to a ventricular septal defect, there will be cardiomegaly and increased pulmonary vascular markings.[30] There also may be significant cardiomegaly in the presence of left AV valve regurgitation.

Electrocardiogram

The electrocardiogram may give the most significant clue to the diagnosis of ventricular inversion. The presence of reversed septal depolarization[41] (i.e., Q waves over the right precordium with absent Q waves over the lateral precordium in the presence of any degree of AV block) but, in particular, complete heart block should immediately suggest ventricular inversion.[17,42] The particular reversal of septal depolarization in the absence of other electrocardiographic criteria of right ventricular hypertrophy also is highly suggestive of this defect.[9,41,43] As with the other clinical features, the associated defects may affect the electrocardiogram and make the diagnosis less obvious.[44]

Echo/Doppler

The advent of two-dimensional echocardiography with interfaced pulsed and continuous wave Doppler ultrasound has improved the accuracy of the noninvasive diagnosis of ventricular inversion and its associated abnormalities substantially. The echocardiographic examination of these patients should be performed in a sequential manner, with identification of the relation and connection of each cardiac segment.[10]

Several major anomalies should alert the echocardiographer to the presence of ventricular inversion. First, there is difficulty in alignment of the intracardiac structures in the usual echo views. In patients with ventricular inversion, the positioning of the heart within the chest and the relationship of the ventricles to each other differs considerably from normal.[45] Additionally, there is discontinuity between the left AV valve and the aortic or left-sided semilunar valve.[10,46] Another prominent feature of atrioventricular discordance is attachment of the left AV valve more inferiorly along the ventricular septum than the right AV valve. This feature is often thought of as the echocardiographic hallmark of atrioventricular discordance but may not be demonstrable if an inlet ventricular septal defect is present, as occurs in many cases.

Other echocardiographic criteria are useful in distinguishing ventricular and AV valve morphology. When chordal attachments of an atrioventricular valve to the inlet septum are present, that atrioventricular valve is almost invariably a tricuspid valve, and the ventricle into which it empties is the right ventricle. Demonstration of such chordal attachments is helpful in confirming that a ventricle is indeed the right ventricle.[45] Conversely, the absence of such attachments indicates that the atrioventricular valve in question is a mitral valve and that the ventricle to which it connects is a left ventricle.

The presence of a left ventricle is suggested by an inlet valve with a bicommissural or "fishmouth" appearance, two discrete papillary muscles, fine trabeculations, and an ellipsoid shape. The presence of a right ventricle is suggested by an inlet valve with a triangular (tricommissural) appearance, multiple irregular papillary muscles, a coarse trabecular pattern, and a roughly triangular shape.

The abnormal atrioventricular connections can be clarified once the ventricular morphology has been identified. Finally, the abnormal relative relationship of the two semilunar valves to each other in these patients and the abnormal course of their great arteries should be demonstrated to support the diagnosis of ventricular inversion with transposition of the great arteries. Obtaining multiple short-axis cross sections through the ventricular outflow tracts is an effective way to demonstrate their orientation and the course of the great arteries.

Many malformations associated with atrioventricular discordance can be shown echocardiographically. Particular attention should be given to evaluation for ventricular septal defects, for pulmonary valve and subvalvular obstruction, and for displacement of the tricuspid valve into the right ventricle. The location and size of ventricular septal defects can be estimated by direct imaging. Two-dimensionally directed pulsed and color Doppler are often helpful in this assessment. Continuous-wave Doppler can assist in estimation of pressure gradient across ventricular septal defects and across the left ventricular outflow tract. Displacement of the tricuspid valve into the right ventricle is visualized readily with two-dimensional echocardiography, and associated valvular insufficiency can be detected by pulsed and continuous-wave Doppler. When multiple defects are present (such as ventricular septal defect and pulmonary stenosis), Doppler studies, particularly continuous-wave Doppler, should be interpreted cautiously. Detailed echocardiographic studies are often helpful in determining when further and more definitive studies will be indicated, particularly if the symptomatology suggests surgical intervention.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis depends upon the associated defects. A patient with ventricular inversion, transposition of the great arteries, and no other defects may appear normal for years.[7,10,27] Even so, physical examination should raise suspicions of some abnormality and suggest the possibility of pulmonary hypertension because of the loud single second heart sound.[30]

In the rare infant who presents with ventricular inversion and normally connected great arteries, the presentation is one of severe cyanosis and is similar to that of infants with transposition of the great arteries with normal atrioventricular relations.[29,47] Isolated ventricular inversion is so rare, it probably should not be considered until at least the echocardiogram or catheterization data are available.

More often, patients present with the findings of a somewhat atypical ventricular septal defect or ventricular septal defect with pulmonary stenosis.[24] The loud second heart sound always suggests associated pulmonary hypertension. The peculiar electrocardiogram and often unusual roentgenogram should immediately sug-

gest the ventricular inversion/transposition complex in addition to the more usual lesions.

CARDIAC CATHETERIZATION

Although the diagnosis should be suspected from the clinical findings and many of the details of the associated defects described by echocardiography, the definitive diagnosis in ventricular inversion regardless of associated defects should be by cardiac catheterization with high-quality selective cineangiocardiograms. Catheterization should aim to acquire all the minute details of the anatomy and precise hemodynamics—not just to verify or identify the general anatomy and basic associated defects. Prior to catheterization of these patients, one should devise a plan of what data are needed and ways to obtain these data. If one undertakes the catheterization of these patients, it should be with the idea that all chambers and vessels will be entered and valid measurements of pressure and oxygen saturation obtained from each location.

The difficulty in entering the pulmonary artery by the usual manipulations with the catheter and the catheter course once one has entered a great artery immediately suggest ventricular inversion—even in the unlikely situation in which it was not suspected before catheterization. The catheter passage from the right atrium to the left ventricle is relatively easy and similar to the maneuver in the normal heart. But the similarity ends here. There is an approximate 180° turn from the inflow of the left ventricle to the outflow into the pulmonary artery with the outflow directed medially and posteriorly to the patient's right. Often with an associated ventricular septal defect, the usual "right heart" catheter manipulations will result in the catheter's passing through the ventricular septal defect and into the ascending aorta. Because of the peculiar angle into the pulmonary artery and problems with the conduction system to be mentioned later, in this situation the use of a diagnostic floating balloon catheter may be indicated as the initial catheter for the study.

With the high probability of tricuspid valve abnormalities, the left atrium must be entered both for hemodynamic measurements across this valve and for high-quality angiography in the left atrium. Fortunately, the atrial relationships to each other and the interatrial septum are relatively normal so that a standard transseptal approach makes entry into the left atrium very straightforward should the patient have an intact atrial septum.

Angiocardiography

High-quality, selective angiocardiograms provide the essential definitive anatomic information in these patients.[48] The basic anatomy is demonstrated best by selective ventricular angiocardiograms in each ventricle using at least 1 cc/kg of contrast delivered in one heart beat. If an associated ventricular shunt lesion is suspected or known, twice this much contrast may be necessary. Because of the peculiar abnormal orientation of the interventricular septum in these patients, the best initial view is in the straight posterior–anterior and lateral projections. This will usually cut the ventricular septum on edge and, if there is a ventricular septal defect, outline it well. The posterior–anterior projection will define the right ventricle and separate the inflow and outflow areas of the ventricle. The left ventricle is stretched out almost in its longest dimension in this view. If, in any particular patient, some additional peculiar orientation of the anatomy is noted on the first angiocardiogram, then adjustment and modification of the projections to best suit the individual patient must be made on the basis of the original injection and not on previously prescribed angled views.[10,49]

The ventricular angiocardiograms should provide valuable information about the AV valves and suggest the ideal projections to use for more selective atrial angiocardiograms to look at these valves.

Extra Risks to Cardiac Catheterization

With ventricular inversion, the AV conduction system is more "fragile" than in hearts with normally related ventricles. Structurally, the common AV bundle remains on the left ventricular side of the septum immediately beneath the pulmonary valve; in this case of the commonly associated ventricular septal defect, the conduction system courses anteriorly around the upper rim of the septal defect. This places the already-fragile bundle in a precarious position on the "working" side of the usual right heart catheterization and directly in the path of the catheter tip as it is manipulated anteriorly and cephalad toward the outflow tracts. Complete and permanent heart block has occurred with the first manipulation of the catheter from the right atrium into the left ventricle, and at least transient complete heart block occurs commonly following any manipulation in the left ventricle. To minimize trauma in the region of the outflow tract, the use of a floating balloon catheter during the manipulations of the diagnostic "right heart" catheterization is recommended.

Therapeutic Catheterization

The rare newborn infant with ventricular inversion and normally connected great arteries, like the infant with transposition of the great arteries and atrioventricular concordance, has transposition physiology with parallel pulmonary and systemic circulations. Similarly, these infants are dependent upon intracardiac mixing through some additional defect for survival and, in the absence of a preexisting atrial septal defect, should undergo an emergency balloon atrial septostomy.

MANAGEMENT

No therapy is necessary for the patient with ventricular inversion and transposition of the great arteries and no other cardiac defect. These extremely rare patients are corrected physiologically and have been reported to have near-normal life expectancy. However, most cases of ventricular inversion with transposition have other associated defects, which often require earlier therapeutic intervention.

Conservative

The management of these patients should be predicated predominantly on symptoms rather than the theoretical improvement that might be made in their hemodynamics. In determining therapy, one should always be reasonably sure that the patient will be *symptomatically* improved by the therapy. This is because the surgical approach is more difficult, frequently leading to a poor hemodynamic result; also, complete heart block is very likely to result. The exception to this rule is when there is significant objective deterioration in the functional capacity of the heart that has not yet caused overt symptoms or when there is a potentially life-

threatening situation. Examples of this would be progressive right ventricular dilation and decreased right ventricular function due to left AV valve insufficiency yet no overt symptoms of pulmonary congestion or "left-sided" heart failure, or complete AV block with a very slow ventricular response yet not causing syncope. The patient with a ventricular septal defect and markedly elevated pulmonary artery pressures that would probably lead to pulmonary vascular disease would require surgical intervention.

Surgical

There probably should be no elective surgery for the defects associated with ventricular inversion and transposition of the great arteries. Although better results recently have been reported,[50] these address primarily survival of the surgery rather than long-term functional improvement. Surgical therapy of even the simple but commonly associated defects such as the ventricular septal defect or the pulmonic stenosis carry a much higher surgical morbidity (and even mortality) as well as even higher likelihood of being unsuccessful in improving functional capacity.

Although the ventricular septal defect is usually in the perimembranous location, surgery is hampered by lack of any direct approach to the defect. Because the right ventricle serves as the systemic ventricle, one should not open this chamber. A ventriculotomy into this chamber creates damage to this already embryologically compromised systemic ventricle. The left-sided atrioventricular tricuspid valve usually is abnormal congenitally and, as a result, is marginally effective as a systemic atrioventricular valve as well. It also connects the *left* atrium with the right ventricle, making the technical considerations to any approach to the ventricular septal defect through the tricuspid valve difficult if not impossible. The recommended approach to the ventricular septal defect is through the mitral valve, either by displacing the septal leaflet or, more often, incising the mitral valve at the annulus to approach the ventricular septal defect and then resuturing the mitral valve after the ventricular defect is closed. In addition to the difficult exposure and potential for permanent mitral valve damage, this approach places the surgery on the AV node side of the septum, requiring that the patch on the ventricular defect be sewn through the defect on the opposite, or right ventricular, side of the septum.[51,52] Even this difficult approach frequently does not protect the AV node and conduction system, and AV block results.

The pulmonary stenosis creates an even greater problem.[53] The stenosis is usually subvalvular; this area is relatively posterior within the heart, with the right ventricle overlying it anteriorly and to the left and the anterior leaflet of the mitral valve guarding the area from the right approach. In addition, the AV conduction system runs in this vicinity on the left ventricular side of the septum and even tension on the valve apparatus before any surgical excision of tissue has produced atrioventricular block. Experience has been so poor with any direct approach to this area that the accepted approach to the subvalve pulmonary obstruction now is by an interposition conduit from the apex or wall of the left ventricle to the pulmonary artery.

Indications for tricuspid valve replacement in patients with ventricular inversion are similar to those for mitral valve replacement in a patient with normal atrioventricular connections.[53] Technical problems of a proper valve insertion are similar to those in the Ebstein's malformation of the tricuspid valve in patients without ventricular inversion and are further indication to delay this surgical procedure for as long as possible without compromising right ventricular function.

The rare patient with ventricular inversion and normally connected great arteries, ironically, is the best candidate for surgical correction. A standard venous switch (Mustard or Senning) procedure performed early will physiologically and almost anatomically correct these patients by redirecting the systemic venous blood into the right ventricle, which gives rise to the pulmonary artery, and redirecting the pulmonary venous blood into the left ventricle, which opens to the aorta. This is the only situation in which relatively early and elective surgery should be considered in patients with ventricular inversion.

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CHAPTER 74

Single Ventricle

Edward V Colvin

This chapter concerns a group of hearts unified by certain similarities and divided by significant differences. Controversy persists concerning which similarities should allow inclusion of an individual heart within the group, which differences should be used for subclassification, and which terms are most useful in describing the hearts.

Case reports in the 1800s and earlier drew attention to the existence of hearts with one large chamber in the ventricular mass. Often a second, much smaller chamber was recognized. An interesting anecdote in the history of pediatric cardiology centers around a case of a single ventricle. The new curator at the medical museum of the McGill Medical School in Montreal, Dr. Maude Abbott, wrote the former curator with questions about the unusual specimen with only one ventricle. Dr. William Osler answered that the specimen was from a 22-year-old man who had had moderate cyanosis since childhood that increased on exertion. The man had episodes of chest pain with shortness of breath and died during one of these episodes. Dr. Osler indicated that the case had been reported by Dr. Andrew F. Holmes, the first dean of the medical faculty of McGill University. Dr. Osler encouraged Dr. Abbott to report the "Holmes heart" again and to write the section on congenital cardiac disease in his famous textbook, *The Principles and Practices of Medicine*. This unusual single-ventricle specimen began the career of Dr. Abbott in the study of congenital heart disease, which was instrumental in the development of the field of pediatric cardiology. The "Holmes heart" is discussed later in this chapter.

Over the years various names have been applied to such single-ventricle hearts[1,2] (Table 74–1). Despite the fact that in most of these hearts there were two chambers within the ventricular mass, "single ventricle" became the most commonly used name.[3]

In 1964, Van Praagh, Ongley, and Swan[4] described a group of these hearts. The criteria for inclusion was the presence of a chamber receiving either both tricuspid and mitral valves or a common atrioventricular valve. Hearts with tricuspid or mitral atresia were specifically excluded. The terms single ventricle and common ventricle were used interchangeably but frequently the presence

Table 74–1. Synonyms for Single Ventricle

Both auricles opening into the left ventricle
Cor triloculare biatriatum
Hearts with one ventricle
Cor biatrium triloculare
Cor biloculare and cor triloculare
Functional cor triloculare biatria
Holmes heart
Heart with two cavities
Single ventricle with a diminutive outlet chamber
Common ventricle
Functional cor biatrium triloculare
Univentricular heart
Triloculate and biloculate hearts
Single ventricle with a rudimentary outlet chamber
Cor triloculare biatriatum
Double-inlet left ventricle
Primitive ventricle
Apparently single ventricular chamber
Double-inlet right ventricle

After Van Praagh, R., Plett, J.A., Van Praagh, S.: Single ventricle: Pathology, embryology, terminology, and classification. Herz, *4*:113–150, 1979.

of an outlet chamber was acknowledged. Hearts were divided into types A through D according to ventricular morphology, and subdivided into groups I through IV according to the relative positions of the arterial valves (Fig. 74–1). "The principal ventricular malformation in each type is absence of the right ventricular sinus (type A); absence of the left ventricular sinus (type B); absence, or rudimentary development, of the sinus portion of the ventricular septum (type C); and absence of both right and left ventricular sinuses, and hence, also of the ventricular septum (type D)."[4] The relationships between the great arteries were described as normal (type I), d-transposition (type II), l-transposition (type III), and inversus (type IV). The most common form of single ventricle would be called type A III. Lev et al.[5] reported a second series of hearts, accepting the definition of single ventricle on the basis of the entrance of both atrioventricular valves or a common valve into a single ventricle.

Other authors pointed out the similarity within the ventricular mass of hearts classified as single ventricles and other hearts excluded from this grouping because of an absent or imperforate right or left atrioventricular (AV) valve.[6–10] Surgical techniques developed for separating the systemic and pulmonary circulations in tricuspid atresia[11,12] were successfully applied to hearts with right and left AV valve atresia and to hearts fitting Van Praagh's definition of single ventricle.[13]

Because of the similarities in ventricular architecture and surgical intervention, it became desirable to group these hearts together. An attempt to do this[14] while preserving the standard English meaning of "single" in the term "single ventricle" led one group to redefine the term "ventricle," ascribing ventricular status to a chamber with inlet and trabecular components, while denying ventricular status to (sometimes larger and more well-formed) chambers with only apical trabecular and outlet components. To deal with the hearts in which an atrium was connected to more than one chamber in the ventricular mass (overriding atrioventricular valves) a 50% rule was applied. When an atrium was connected partly to one chamber and partly to another, the inlet was assigned to the chamber in the ventricular mass connected to greater than 50% of the atrium. Thus, a chamber receiving 49% of an atrioventricular orifice was not a ventricle, whereas one receiving 51% was. This violated one of the fundamental precepts of the morphologic method of nomenclature, that each structure should be named according to its own morphology and not according to adjacent structures. Confronted[15,16] with the implications of this redefinition of a ventricle, Anderson et al.[17,18] abandoned this tactic and recognized that they were defining a grouping on the basis of a different selection criterion.

Rather than focusing on the ventricular anatomy they focused on the atrioventricular connection. By this new criterion, a heart is included in the grouping (hearts with univentricular AV connection) if both atria are connected to a single chamber within the ventricular mass. Thus, most hearts classified by Van Praagh as members of the single ventricle group are included, but now the hearts in which both atria connect to a single chamber are included even if one valve is imperforate or atretic. Hearts in which each atrium is connected to its own ventricle are excluded even if one of the valves is atretic or imperforate. These hearts are included in the group of hearts with biventricular AV connection.

In this chapter we will discuss this larger group of hearts defined by the presence of an univentricular AV connection. Tricuspid atresia and mitral atresia will also be discussed in more detail in other chapters.

RELATIONSHIPS BETWEEN THE GREAT ARTERIES

Type	I	II	III	IV
Superior / Right ↔ Left / Inferior / Anterior View	Normal	D-Transposition	L-Transposition	Inversus
Posterior / Right ↔ Left / Anterior / Superior View				
Cases, No. (%)	9 (15%)	25 (42%)	26 (43%)	0

VENTRICULAR MALFORMATIONS

Type	A	B	C	D
Principal Malformation	Absence of RV Sinus	Absence of LV Sinus	Absent or Rudimentary Ventricular Septum	Absence of RV and LV Sinuses and of Ventricular Septum
D-Loop / RV (R) LV (L) / Anterior View				
L-Loop / LV (R) RV (L) / Anterior View				
Cases, No. (%)	47 (78%)	3 (5%)	4 (7%)	6 (10%)

* x - Loop. Two cases with dextrocardia, since ventricular apex posterior
* Dextrocardia

Fig. 74–1. Subclassification of 60 hearts with single ventricle. Ao = aorta; PA = pulmonary artery; AoV = aortic valve; PV = pulmonary valve; RV = right ventricle; LV = left ventricle; Inf = infundibulum; RVM = RV mass; LVM = LV mass. (From Van Praagh, R., Ongley, P.A., and Swan, H.J.C.: Anatomic types of single or common ventricle in man: Morphologic and geometric aspects of 60 necropsied cases. Am. J. Cardiol., *13*:367, 1964.)

NOMENCLATURE

Atrial Situs and Atrioventricular Connection

The segmental approach to nomenclature[19–23] is necessary to describe these hearts. Atrial situs may be solitus or inversus, or there may be atrial isomerism, with bilateral right or left morphology. The axis of the ventricular mass may be leftward (levocardia), rightward (dextrocardia), or midline (mesocardia). The type of atrioventricular connection is, by definition, univentricular. The mode of connection may be double inlet, absent left, or absent right atrioventricular connection. In double inlet the two atria may be connected to the ventricle by means of two separate valves or via a common valve (Fig. 74–2). When two separate valves are present, they usually do not have typical characteristics of mitral and tricuspid valves[5] and are therefore referred to as right and left on the basis of the anatomic location of the atrium to which they are connected. Either of these valves may be stenotic or even imperforate. Since both atria are connected to one ventricle, the connection cannot be termed concordant or discordant.

When one atrium lacks a connection to the ventricles, it is difficult to be certain whether the missing valve would have been mitral or tricuspid. We prefer to use the terms absent left and absent right AV connection to describe these hearts.[24–33]

Hearts with two valves, each connecting an atrium to its own ventricle, are considered to have biventricular atrioventricular connection, even if one of the valves is imperforate. Hypoplastic left

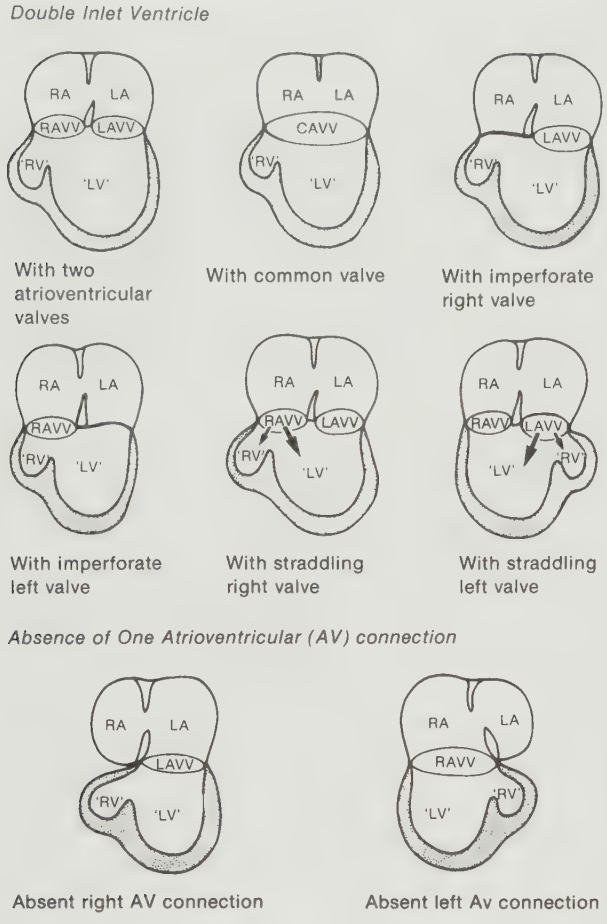

Fig. 74–2. The modes of atrioventricular connection found in a series of hearts with dominant left ventricle. RA = right atrium; LA = left atrium; RAVV = right atrioventricular valve; LAVV = left atrioventricular valve; RV = right ventricle; LV = left ventricle. (From Anderson, R.H., et al.: Ventricular morphology in the univentricular heart. Herz, *4*:184, 1979.)

heart syndrome, in which a hypoplastic or imperforate left AV valve connects the left atrium to a small left ventricle (usually in association with aortic atresia), is excluded from the group of hearts with univentricular AV connection. In pulmonary atresia with intact ventricular septum, there is one large and one small ventricle. Since the AV connection is biventricular, these hearts are also excluded from this grouping.

In any system of nomenclature one must decide how to deal with hearts in which the atrial myocardium is connected to more than one ventricle (overriding of the AV valve annulus) and with hearts in which the tensor apparatus of the AV valve enters both ventricles (straddling). One could consider this a special type of atrioventricular connection and group these hearts as having neither univentricular nor biventricular AV connection.[34,35] Practically, they must be treated by the surgeon as he would treat hearts with univentricular or biventricular connection. The degree of overriding determines the type of connection. By the 50% rule, if more than 50% of the AV connection overrides and connects to the opposite ventricle the connection is considered to be univentricular, otherwise a biventricular connection is said to be present. If straddling of the tensor apparatus is present, the degree must be specifically stated, as this is an important surgical detail.[36] When there is atresia of one valve the remaining valve may straddle.[37] Part of a common valve may straddle. When two AV valves are present, one or conceivably both may straddle.

Ventricular Architecture

In embryologic terms, a complete ventricle has sinus and infundibular (or conus) portions. The embryologic origin of the sinus portion of the right ventricle remains controversial. Use of these terms to describe the ventricular anatomy requires speculation as to the embryologic origin of the different chambers. In more descriptive morphologic terms, a complete ventricle may be said to have inlet, apical trabecular, and outlet components.[38] The inlet component comprises the portion downstream from the atrioventricular valve annulus, whether the valve is patent or imperforate. The anatomical presence of an inlet component is unrelated to the patency of its valve. The trabecular component comprises the body of the ventricle distal to the insertion of the papillary muscles. The outlet component supports the arterial valve of the ventricle. It may be a complete muscular structure or may be attenuated to permit continuity between the arterial and atrioventricular valves.[20] In the normal heart the right and left ventricular chambers have characteristic morphology of inlet, apical trabecular,[39] and outlet portions. In hearts with univentricular AV connection the inlet portion of each chamber is abnormal. The outlet portion may also be abnormal or absent. It is the apical trabecular portion of a ventricle that can usually be used to classify a chamber as being of right or left morphology. In the morphologically right ventricle the apical component has characteristic coarse trabeculations. In the normally constituted right ventricle there is also a prominent muscular elevation, the septomarginal trabecula, on the septal surface. This structure may or may not be present when the right ventricle is incomplete. When it is present, a further array of muscle columns within the apical component extends from its anterior edge to the parietal wall of the ventricle. In contrast, the apical component of the morphologically left ventricle has much finer criss-crossing trabeculations and a smooth septal surface.

When two chambers are found within the ventricular mass, one has a right and the other has a left ventricular apical trabecular component. The ventricle receiving the AV valve or valves is usually larger and termed the dominant ventricle. The other ventricle may be described as nondominant, rudimentary, or incomplete. This nondominant ventricle is usually small, but there is considerable variability in its size. We have described this variability as mild, moderate, or severe dominance.[40] Anderson[2] has graded the hypoplasia of the nondominant ventricle in a similar manner, as mild, moderate, or severe. One must also note which components are present in this incomplete ventricle. The apical trabecular component is present and the inlet absent or nearly absent by definition—the presence of the outlet must be specified. The shorthand terms "outlet chamber" and "trabecular pouch" were invented to describe incomplete ventricles without calling them ventricles. These terms describe a nondominant ventricle with and without an outlet component, respectively. Because they are brief and descriptive, their use as verbal shorthand will likely continue.

While the dominant ventricle usually contains all three components, it may lack an outlet component. Hearts have been described with double-inlet left and double-outlet right ventricles.[21]

The relationship of the two ventricles in space is an important variable and must be specified in some manner. In hearts with biventricular AV connection, this has been specified by various authors as d- or l-loop, right- or left-hand ventricular architecture, noninverted or inverted ventricles. In most hearts with univentricular AV connection a similar distinction can be made. In a heart with right-hand morphology it is only possible to place the palmar surface of one's right hand on the septal surface of the right ventricle such that the thumb is in the inlet, the fingers in the outlet and the wrist in the apical trabecular component (Fig. 74–3). In a heart with left-hand morphology only the left hand will fit in this manner in the right ventricle. This method of determining the relative positions of the two ventricles fails when the right ventricle has no inlet component to accept the thumb. Stefanelli et al.[41] suggested using the reverse rule in the left ventricle in this case. However, in some hearts the nondominant ventricle may lie directly anterior or posterior to the dominant ventricle. In such cases, a "long-hand" description of relative positions is required.

When two ventricles are present the communication between them is properly termed a ventricular septal defect. The term outlet foramen was promoted by Anderson for cases in which the second chamber was denied ventricular status and it would have been illogical to call this communication a ventricular septal defect. Outlet foramen is a descriptive term and will probably continue to be used. The term "bulboventricular foramen" is of embryologic origin and its use implies that the communication between the two chambers in the mature heart is a persistence of the bulboventricular foramen in the embryonic heart. The implication is that the nondominant chamber is totally of bulbar origin, while the dominant chamber originates from the primitive ventricle. This term is less appealing since its use requires speculation as to the abnormal embryology.

Rarely, a heart is encountered that has a trabecular pattern typical of neither a right nor a left ventricle and in which, despite axial angiography and microscopic sectioning, no second ventricular chamber can be found. Such ventricles are said to have indeterminate ventricular morphology.

Other hearts have been described in which the ventricular mass contains a trabecular pattern typical of a right ventricle on one side and of a left ventricle on the other, with only a tiny rim of apical ventricular septum. Lev[5] used the term "common ventricle" to describe these hearts. Van Praagh[4] included them in his classification as type C. In the most recent work of Anderson[21] these hearts are considered to have biventricular AV connection with a large ventricular septal defect. They are excluded from the group of hearts with univentricular AV connection. Surgical considerations, however, may be similar to hearts with univentricular AV connection. The correlation between Anderson's terminology and Van Praagh's is given in Table 74–2.

The ventriculoarterial connections must be specified. If two great vessels are present, the connection may be concordant or discordant (normally related or transposed, relative to the ventricular septum), or double outlet from one ventricle may be present. Single outlet may be present with a common arterial trunk, or in cases with aortic or pulmonary atresia. When two great vessels are present it is useful to specify their relative location as well as the ventriculoarterial connection.

ANATOMY

Ventricular Anatomy

Hearts with univentricular AV connection may be subdivided, according to ventricular morphology, into three basic types: hearts with dominant left, dominant right, or indeterminate ventricular morphology. Dominant left or dominant right ventricular morphology can occur with right hand (d-loop) or left hand (l-loop) architecture (Fig. 74–4).

The most common type has a dominant ventricle with an apical trabecular portion of left ventricular type, called double-inlet left ventricle (or, by Van Praagh,[1] single left ventricle). The nondominant ventricle has an apical trabecular portion of right ventricular type. It is usually located anteriorly to the left or right but occasionally is located directly anteriorly. It almost always gives rise to one or both of the great vessels.

Hearts in which the dominant chamber possesses an apical trabecular portion of right ventricular type have been called double-inlet right ventricle (or, by Van Praagh,[1] single right ventricle). The nondominant ventricle has an apical trabecular component of left type and is located posteriorly, usually either more to the left or right. Most commonly, this chamber has neither inlet nor outlet components, though many cases have been documented with outlet of a great vessel from this ventricle. Recognition of hearts with dominant right ventricles often depends on the identification of

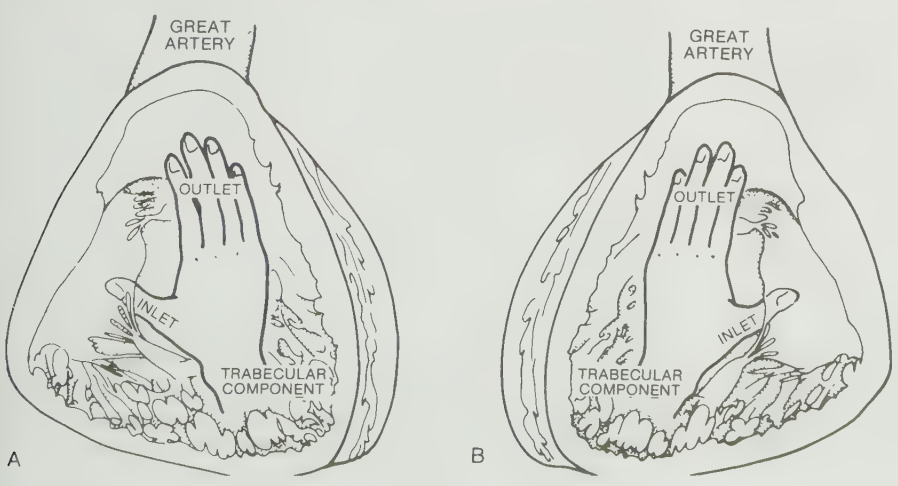

Fig. 74–3. Illustration of the right-hand rule for describing ventricular architecture. A) Right-hand architecture. B) Left-hand architecture. (From Anderson, R.H., Becker, A.E., Tynan, M., and Wilkinson, J.L.: Definitions and terminology—The significance of sequential segmental analysis. *In* Double Inlet Ventricle. Edited by R.H. Anderson, G. Crupi, and L. Parenzan. Tunbridge Wells, Kent, Castle House Publications, 1987.)

Table 74–2. Comparison of Terminology Used by Different Groups

Becker et al. (1987)	*Van Praagh et al. (1964)*	*Ritter et al. (1979)*
Double-inlet left ventricle	Single ventricle type A	Common ventricle type A
With rightward RV and VA concordance	Type A1	Type A1
With leftward RV and VA concordance	—	—
With rightward RV and VA discordance	Type A2	Type A2
With leftward RV and VA discordance	Type A3	Type A3
Double-inlet right ventricle	—	—
With left-sided rudimentary LV	—	—
With right-sided rudimentary LV	—	—
With rudimentary ventricle	Single ventricle type B	
Double-inlet indeterminate ventricle	Single ventricle type D	Common ventricle type C (without outlet chamber)
High ventricular septal defect	Single ventricle type C	

RV = right ventricle; VA = ventriculoarterial; LV = left ventricle.

From Becker, A.E., Anderson, R.H., Penkoske, P.A., Zuberbuhler, J.R.: Morphology of double inlet ventricle. *In* Double Inlet Ventricle. Edited by R.H. Anderson, G. Crupi and L. Parenzan. Tunbridge Wells, Kent, Castle House Publications Ltd, 1987.

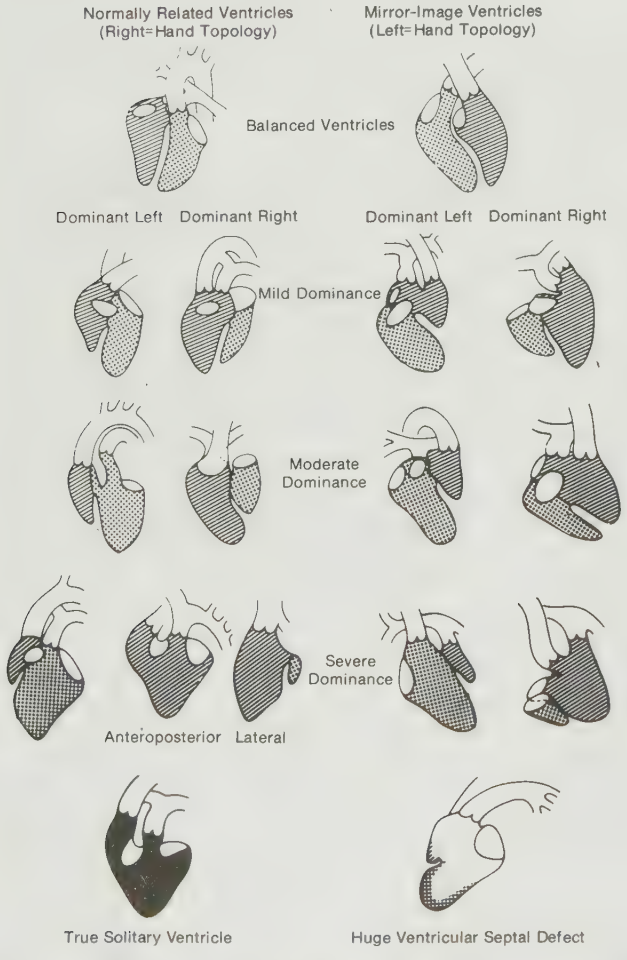

Fig. 74–4. Spectrum of hearts with one large and one small ventricle. Each heart is traced from an actual angiogram. (From Bargeron, L.M.: Angiography of double inlet ventricle. *In* Double Inlet Ventricle. Edited by R.H. Anderson, G. Crupi, and L. Parenzan. Tunbridge Wells, Kent, Castle House Publications, 1987.)

the (usually small) nondominant left ventricles. In vivo this requires high-resolution two-dimensional echocardiography or axial cineangiography. Postmortem identification may require microscopic examination.

Hearts in which only one abnormally trabeculated ventricle can be found are termed hearts with univentricular AV connection and indeterminate ventricular morphology, or by Van Praagh[1] "single ventricle with morphologically undetermined myocardium." Van Praagh expressed doubt that these hearts are different from single right ventricle. Anderson et al.[21] note differences in coronary artery, conduction system, and internal ventricular architecture that support the distinction of these hearts from hearts with dominant right ventricle.

Dominant Left Ventricle

In hearts with a dominant ventricle of left morphology the ventricular septum is displaced anteriorly and does not extend to the crux of the heart. The coronary arteries usually arise from the two aortic sinuses that face the pulmonary trunk. Both right and left coronary arteries give off anterior delimiting branches that provide an external guide to the location of the septum.[5,42] Rarely, a portion of the chordal apparatus of one of the AV valves will insert into the right ventricle. Almost always either the aorta or the pulmonary artery will arise from the right ventricle; rarely, both great vessels or a common arterial trunk will.[43] The communication between the dominant left and nondominant right ventricle is via a ventricular septal defect, occasionally via multiple ventricular septal defects.[44] The ventricular septal defect may or may not be restrictive.[45]

Right-hand Architecture. The Holmes heart is a classic member of this group of hearts. Holmes[46] described this heart in 1824 and his description was republished by Abbott[47] in 1936. There was atrial situs solitus and levocardia with normally related ventricles (right-hand architecture). The AV connection was double inlet to a dominant left ventricle and the ventriculoarterial connection was concordant. The pulmonary artery arose from a rightward chamber with the apical trabecular architecture of a right ventricle. Other hearts with similar morphology have been described.[48] Hearts with a common AV valve, a similar ventricular architecture, and ven-

triculoarterial connection have also been referred to as Holmes hearts.[49]

The ventricular septal defect has a tendency to be restrictive in these hearts. In the setting of right AV valve atresia there is a documented tendency for the ventricular septal defect to become smaller.[50–54] The outlet septum is usually extensive enough to allow resection should enlargement of the ventricular septal defect be required. The chordal apparatus of the right AV valve may insert on the left ventricular surface of the outlet septum and limit resection.[45]

The similarity of the ventricular architecture between the Holmes heart, called by all a "single ventricle," and the ventricular architecture of hearts with classic tricuspid atresia was pointed out by Deanfield et al.[7] There followed a controversy in the literature as to whether classic tricuspid atresia should be considered a single ventricle. Van Praagh et al.[16] and Bharati and Lev[55] argued against. In classic tricuspid atresia, they contended, there were two ventricles, while in the Holmes heart there was a single ventricle. Van Praagh et al. distinguish three possible subarterial chambers: right ventricle, left ventricle, and infundibulum. They state "the infundibulum (outflow tract) is demarcated from the right ventricle (inflow tract) by a ring of infundibular (bulbar) muscle formed by the parietal band, the septal band, and the moderator band." They use the entity "double-chambered right ventricle" to illustrate the difference between the right ventricular inflow and outflow (infundibulum).

It is not clear how one distinguishes the trabeculations of the infundibulum from those of the sinus. Becker et al.[56] point out that the "infundibulum" in tetralogy of Fallot typically comprises only an outlet. It would seem that there is little justification on the basis of the morphologic method for calling the typical nondominant chamber in a heart with a dominant left ventricle, an infundibulum rather than a right ventricle. Of course, it does logically allow one to call hearts with double inlet to a dominant left ventricle, "single ventricle," since the infundibulum is not considered a ventricle. This seems as contrived as the attempts of Anderson to rename the same structure an "outlet chamber" to avoid calling it a ventricle. Again, the problem is trying to preserve the literal meaning of the term single ventricle for a heart that clearly has two chambers within the ventricular mass.

Anderson et al. initially called both the Holmes heart and classical tricuspid atresia, univentricular hearts,[57] denying ventricular status to the nondominant chamber, which they called an outlet chamber in both lesions. Subsequently, they modified their approach to this group of hearts by focusing on the AV connection. They then called the right-sided chamber in both hearts a ventricle. Neither heart would literally have a single ventricle, but both would be included in the group of hearts with univentricular AV connection.

Hearts similar to the Holmes heart but with ventriculoarterial discordance have been described. The outlet septum in these hearts is said to be short, limiting resection of muscle to enlarge the ventricular septal defect. In study of hearts of this type in the Pittsburgh autopsy collection, the ventricular septal defect was found to be crossed by bars of muscle dividing the ventricular septal defect into several subdefects.[56] These bars might have compromised flow through the defect and it might have been desirable to remove them. However, from gross examination the conduction axis appeared possibly to descend through one of the bars.

Left-hand Architecture. The paradigm of single ventricle is called by Van Praagh "single left ventricle," and by Anderson "double-inlet left ventricle." There is left-handed ventricular architecture (l-loop) and ventriculoarterial discordance. There is usually situs solitus of the atria with entrance of both AV valves into a large ventricle with the apical trabecular pattern of a left ventricle. The trabecular pattern in the inlet portion is coarser than a usual left ventricle, and the fine trabecular pattern is only well expressed at the apex. There is usually, but not always, a prominent ridge of muscle at the site where the inlet septum would be expected. It does not carry the conduction tissue. The tensor apparatus of the two AV valves is usually segregated into right and left sides. The nondominant ventricle with apical trabecular component of right ventricular pattern is located anterosuperiorly and to the left with respect to the dominant left ventricle. The ventricular septum is displaced anterosuperiorly and does not reach the crux of the heart. The apical trabeculations of the nondominant chamber have the appearance of those in the right ventricle. The remnants of the septomarginal trabecula can often be distinguished on the septal surface. The two ventricles are connected by a ventricular septal defect (rarely multiple ventricular septal defects), which may or may not be restrictive. The pulmonary artery typically arises from the dominant left ventricle, often with associated valvar or subvalvar pulmonary stenosis. The aorta usually arises from the right ventricle anteriorly and to the left of the pulmonary artery. The subaortic outlet septum tends to be short.

If there is an overriding or straddling valve, the septum involved is an anterosuperior structure and the valve overrides its posterior part usually on the same side as the nondominant ventricle.[56] When there is a common valve it is important to try to distinguish the relationship of the atrial and ventricular septal structures. In a typical atrioventricular septal defect with left ventricular dominance the two septal structures are said to align, normally meeting at the crux with the conduction system normally positioned. In double-inlet left ventricle with a straddling common AV valve, the two septal structures do not typically meet[58] and the conduction-tissue axis is abnormally positioned (Fig. 74–5).

While dominant left ventricle with left-hand architecture is most commonly associated with ventriculoarterial discordance, concordant connection has been described. Freedom et al.[59] described these hearts as isolated ventricular inversion with double-inlet left ventricle. Van Praagh[1] has also described cases. In the Children's Hospital of Pittsburgh collection, 3 of 33 hearts with double-inlet left ventricle had this anatomy.[56] In two, there was fibrous continuity between aortic and the atrioventricular valves, while in two, muscle separated these structures.

Dominant Right Ventricle

The dominant chamber receiving the AV connection has rather coarse apical trabeculations and septomarginal trabecula on its septal surface.[14] In our experience and that of others,[56] it is almost always possible to find a small nondominant ventricle of left ventricular morphology. Van Praagh[4] and Lev[5] and their colleagues excluded from the category "single ventricle" hearts with a dominant ventricle of right morphology in which a small left ventricle could be found. Subsequently, Van Praagh has included hearts with a small left ventricle in his definition of single ventricle.

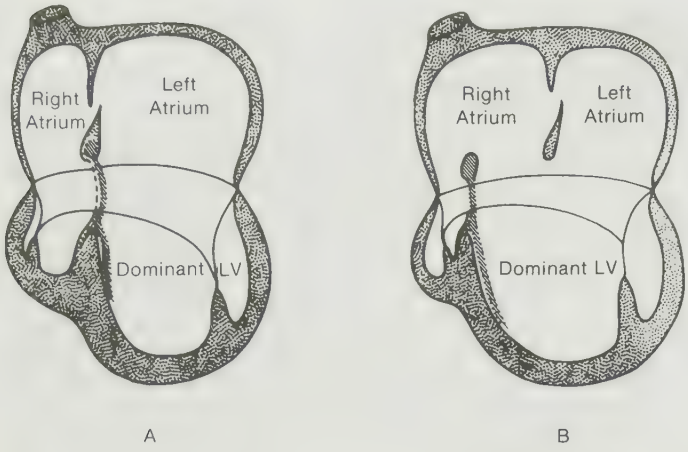

Fig. 74–5. A) Atrioventricular septal defect with left ventricular dominance. B) Double-inlet left ventricle with a straddling common valve. Note the malalignment of atrial and ventricular septal structures. LV = left ventricle; RV = right ventricle. (From Becker, A.E., Anderson, R.H., Penkoske, P.A., and Zuberbuhler, J.R.: Morphology of double inlet ventricle. *In* Double Inlet Ventricle. Edited by R.H. Anderson, G. Crupi, and L. Parenzan. Tunbridge Wells, Kent, Castle House Publications, 1987.)

When a second ventricle can be found, it is almost always posteroinferior to the dominant right ventricle. The ventricular septum extends to the crux and allows application of the right-hand/left-hand rule to distinguish topology. Anterior and posterior descending coronary arteries delimit the position of the posteroinferior nondominant ventricle. In cases with very small chambers these arteries may guide the examiner to the small chamber.[5,14]

From a surgical viewpoint, there is no natural plane of cleavage between the sides of the heart, as is the rule in double-inlet left ventricle. There is no posterior muscular ridge. This makes an operation to divide the dominant right ventricle less attractive.

Right-hand Architecture. Right-hand architecture is by far the most common, with the nondominant left ventricle located posteroinferiorly and leftward. There may be two AV valves, but a common valve is frequently seen. The ventriculoarterial connection is usually double-outlet right, though ventriculoarterial concordance has been reported. Becker[56] reports three common patterns. In the first, there are separate AV valves with the left straddling and double-outlet right ventricle. In the second, a common valve is totally committed to the right ventricle and origin of the aorta is from the nondominant left ventricle. The third exists with right atrial isomerism and is marked by total anomalous pulmonary venous connection and pulmonary atresia. The aorta arises from the dominant right ventricle.

Left-hand Architecture. These hearts are quite rare. There may be two AV valves but usually there is a common valve in the setting of atrial isomerism. The ventriculoarterial connection is usually double-outlet and there may be pulmonary atresia.

Indeterminate Ventricular Morphology

In these hearts the apical trabecular morphology is not typical of either a right or a left ventricle. There is no second ventricle of complementary morphology. One view is that these are hearts of right or left morphology in which the nondominant ventricle has disappeared.[1] Others[56] feel there are anatomic differences that clearly delineate a separate entity. The apical trabeculations are coarser than in the right ventricle and bear no resemblance to a left ventricle. There is no septal surface, either smooth, as typical of a left ventricle or reinforced by the septomarginal trabecula, as in the right ventricle. An abnormal free-standing muscular structure resembling the septomarginal trabecula can sometimes be found in the apical and outlet regions. There often is a posterior ridge of muscle between the two inlet portions that is not typical of double-inlet right ventricle. The coronary arteries can often be used to gain a clue to the location of the nondominant ventricle in hearts with either dominant left or dominant right architecture. In hearts with indeterminate morphology, no prominent descending arteries can be found. There is instead a "wreath" of smaller arteries descending randomly. The conduction tissue is not typical of a heart with a dominant right ventricle.

There is a common association with atrial isomerism, abnormal venous connection, common AV valve, and single outlet with pulmonary atresia. Normal or mirror-image atrial arrangement is also found usually with two AV valves and usually, but not always, with a double outlet from the single ventricle.

Coronary Arteries

The coronary artery distribution is important when an operation requiring ventriculotomy must be performed. The coronary patterns have been described in several reports.[5,7,42,60–62] In the series of Keeton et al.[42] 12 of 17 hearts with double-inlet left ventricle, left-hand architecture and ventriculoarterial discordance displayed a typical pattern. The anterior aortic cusp was the noncoronary cusp. The left coronary artery arose from the left posterior aortic sinus and in 13 of 17 hearts it was the dominant artery. The right coronary artery arose from the right posterior cusp and was the dominant artery in 3 of 17 cases. A major branch, termed a delimiting artery,[63] arose from both right and left coronary arteries. These two delimiting arteries outlined the surface boundaries of the anterior nondominant right ventricle. The right delimiting artery was almost always larger than the left in the postmortem study of Keeton, but in an angiographic study[60] the left was said to be larger. As the main coronary arteries continued in the atrioventricular groove they gave off two to six large branches parallel to the delimiting artery. Variations to the typical anatomy occurred in 5 of the 17 hearts (Fig. 74–6) studied by Keeton.

Keeton examined three hearts with double-inlet left-ventricle, right-hand architecture with ventriculoarterial discordance. Two had typical delimiting arteries. In the other, the right coronary arose from the left anterior cusp and crossed the front of the heart with no delimiting arteries. A single heart with double-inlet left-ventricle, right-hand architecture and ventriculoarterial concordance (Holmes heart) was found to have normal origin of the coronary arteries with typical delimiting arteries. In contrast to the hearts previously mentioned, the right anterior surface of the ventricle was relatively free of vessels. This is important since a number of the hearts undergoing a ventriculotomy for a septation operation suffered transection of possibly important coronary branches.

Deanfield et al.[7] examined the coronary anatomy in postmortem specimens with double-inlet left ventricle, with classic tricuspid atresia, and with pulmonary atresia intact septum. Of the hearts with pulmonary atresia intact ventricular septum, 93% had the posterior extent of the ventricular septum delimited by a coronary

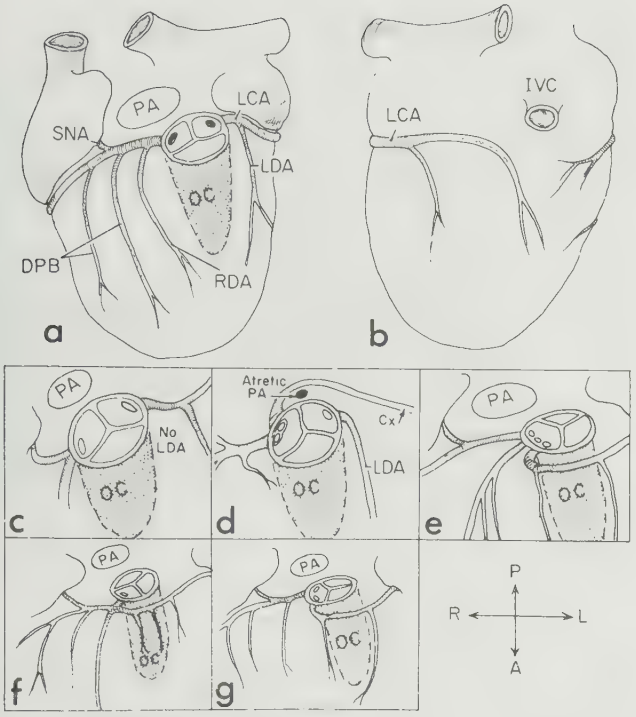

Fig. 74–6. Variations in coronary artery anatomy seen with dominant-left-ventricle and left-hand architecture: a) anterior view; b) posterior view of typical pattern; c) through (g) atypical patterns. SNA = sinus nodal artery; PA = pulmonary artery; LCA = left coronary artery; OC = outlet chamber; LDA = left delimiting artery; DPB = delimiting parallel branch; RDA = right delimiting artery; IVC = inferior vena cava; Cx = circumflex artery; R = right; P = posterior; A = anterior; L = left. (From Keeton, B.R., et al.: Anatomy of coronary arteries in univentricular hearts and its surgical implications. Am. J. Cardiol., *43*:569–580, 1979.)

artery descending at the crux. In contrast, in the hearts with double inlet, and those with tricuspid atresia, the posterior extent of the septum was marked by a delimiting artery descending at the acute margin rather than at the crux. Additional parallel arteries between the delimiting artery and the crux were also seen in most of these specimens.

Conduction System

The anatomy of the specialized conduction system is of great surgical importance in hearts with univentricular AV connection. Observations would suggest that the formation of a normal AV conduction system requires the development of the inlet portion of the ventricular septum to bring the sheet of conduction tissue astride the trabecular portion of the developing septum, into contact with the atrial conduction tissue at the level of the central fibrous body. If this process fails to occur, an abnormal conduction system will develop. The ring of specialized tissue associated with the atrioventricular valve ring is capable of forming a node (or nodes) in association with a penetrating bundle at sites other than the site of the normal AV node. Usually the abnormal node is formed in the anterior or anterolateral portion of the right atrial portion of the AV valve ring. The relation of the two ventricles has a great effect on the location of the contact between the ventricular septum and the conduction tissue associated with the AV valve ring. Hearts with similar ventricular relation in general have similar AV conduction systems. The mode of atrioventricular connection does affect the location of the AV node, particularly in the hearts with absence of one AV valve. The atrial situs also affects the sidedness of the sinoatrial and AV nodes in normally related and inverted atrial relations. When the atrial relations are ambiguous,[64] the sinoatrial node is abnormal—dual with bilateral right-sidedness, hypoplastic with bilateral left-sidedness. In either case, there may be dual AV nodes connected by a sling of specialized conduction tissue.

The description of the conduction system in the various hearts will be organized according to ventricular relationships and subgrouped by mode of AV connection. Normal atrial situs may be assumed unless specifically stated otherwise.

Right-hand Architecture

Dominant Left Ventricle. When the ventricles are normally related and there is left ventricular dominance, the nondominant right ventricle is located anteriorly and to the right. The ventricular septum does not extend to the crux of the heart but meets the AV valve ring more rightward and anteriorly than usual. When there is double inlet (as in the Holmes heart), the inlet portion of the ventricular septum is absent and it is the trabecular portion of the ventricular septum that makes contact with the conduction tissue of the AV ring. This leads to the development of an anterior node with a nonbranching bundle that runs along the left ventricular side of the trabecular septum. If approached from an incision on the left side of the left ventricle, the bundle would be seen beneath the ventricular septal defect (Fig. 74–7). If approached from the right ventricle, the bundle would be on the left ventricular aspect rightward, anatomically, and beneath the ventricular septal defect.

When the right AV connection is absent (classic tricuspid atresia) the disposition of the conduction tissue within the ventricles is similar. The position of the AV node was initially reported to be normal.[65] Other observers[66] found the AV node posterolateral to the dimple in the floor of the right atrium; however, in most cases, there was anterior extension of the nodal tissue and in most of these the penetrating bundle took origin from the anterior extension. The bundle was found on the right parietal wall of the main ventricular chamber and was buried in the myocardium, rather than lying on the crest of the septum as it does in a normal heart.

The form and location of the AV nodal tissue is explained by the fact that regular and anterior nodes can only exist in isolation when the right orifice is formed. When the orifice of the right valve is absent, the junction of the trabecular septum moves more toward the crux and the anterior node becomes merged with the regular node (Fig. 74–8).

Absence of the left AV valve usually is associated with left-hand ventricular architecture, and in this situation there is an anterior AV node. When the ventricles are normally related, one would expect an anterior node with a disposition of the ventricular conduction system similar to double inlet as described above.

When straddling occurs, the most likely location of the connecting AV node will be somewhere along the right atrial orifice close to the point of contact between the anterior or posterior limb of the trabecular septum with the AV orifice; with a straddling right AV valve this would be expected to be posterolateral.[67] There

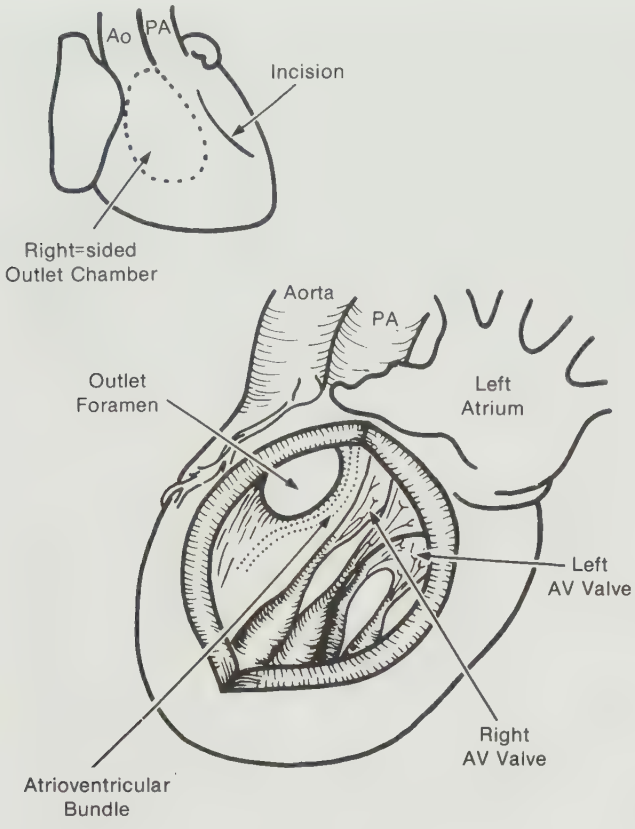

Fig. 74–7. Conduction axis in dominant left ventricle with right-hand architecture, seen from an incision in the dominant left ventricle. Ao = aorta; PA = pulmonary artery; AV = atrioventricular. (From Becker, A.E., Wilkinson, J.L., and Anderson, R.H.: Atrioventricular conduction tissues: A guide in understanding the morphogenesis of the univentricular heart. *In* Etiology and Morphogenesis of Congenital Heart Disease. Edited by R. Van Praagh and A. Takao. Mount Kisco, NY, Futura, 1980.)

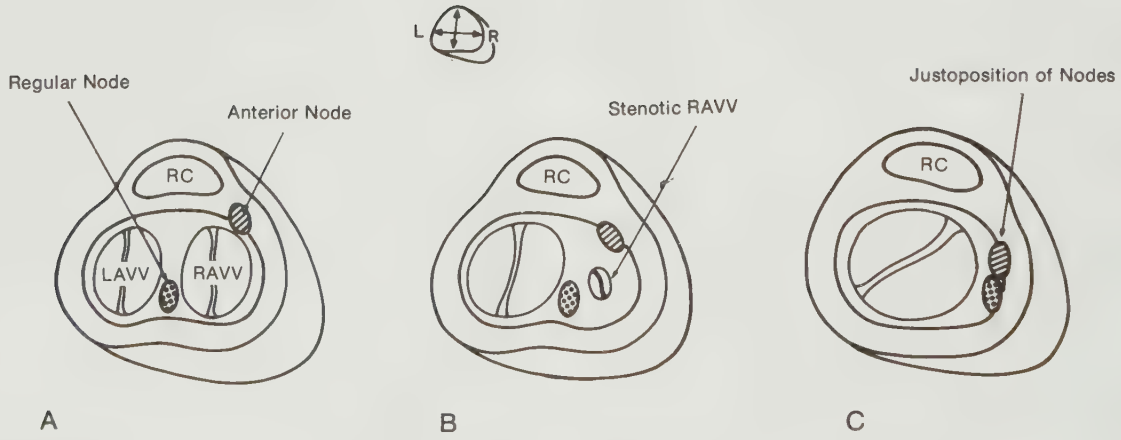

Fig. 74–8. Diagram illustrating how anterior and posterior nodes can only exist as discrete structures when there is a right atrioventricular orifice. With absent connection these two nodes are placed into juxtaposition. A) Double-inlet ventricle; B) double-inlet ventricle, stenotic right atrioventricular valve; and C) absent right atrioventricular connection. L = left; A = anterior; P = posterior; R = right; RC = rudimentary chamber; LAVV = left atrioventricular valve; RAVV = right atrioventricular valve. (From Becker, A.E., Wilkinson, J.L., and Anderson, R.H.: Atrioventricular conduction tissues: A guide in understanding the morphogenesis of the univentricular heart. *In* Etiology and Morphogenesis of Congenital Heart Disease. Edited by R. Van Praagh and A. Takao. Mount Kisco, NY, Futura, 1980.)

is a spectrum of straddling. As the valve becomes more committed to the right ventricle, the posterior extent of the trabecular septum and thus the location of the abnormal node moves more posteriorly toward the crux.[68]

Dominant Right Ventricle. In these hearts the nondominant left ventricle is posterior and to the left. The ventricular septum is presumably mostly trabecular. However, this septum does run to the crux of the heart and may have a component in that area that is similar in embryonic origin to the normal inlet septum. The AV node has been described to be in its normal position with respect to the atrial landmarks.[69] The penetrating bundle usually passes directly onto the septum, though in one case it ran onto a trabecula on the posterior wall.

A case of absent left AV connection with a microscopic left ventricle has been reported.[68] The conduction system was as with double inlet described above. The tiny left ventricle was actually found by following the conduction system on microscopic sections. Presumably, the conduction system with absent left AV connection would be similar to that in double inlet. Straddling would not be expected to alter the conduction system.

Left-hand Architecture

Dominant Left Ventricle. When there is left-hand architecture and a dominant left ventricle, the nondominant right is located anteriorly and to the left. The ventricular septum does not extend to the crux, but is displaced anteriorly and to the left. When there is double inlet, the regular AV node is hypoplastic and does not make contact with the ventricular myocardium. The atrioventricular node and penetrating bundle are anterior and right-sided.[70–72] The penetrating bundle runs an extensive course across the anterior aspect of the outflow tract of the left ventricle then down the right margin of the ventricular septal defect. Bharati and Lev[71] reported two cases in which the entire right atrial roof was formed of node-like tissue, and in one of these the anterior node was divided into two parts. One part gave off the penetrating bundle while the other gave off Mahaim fibers to the ventricular myocardium.

Should the surgeon desire to enlarge the ventricular septal defect, he would resect the margin perceived as inferior when viewed through the right atrium (Fig. 74–9). A previous recommendation that the roof of the defect be resected[73] has been retracted.

It should be pointed out that this discussion assumes a usual ventricular septal defect between outlet and trabecular portions of the ventricular septum. If, as has been reported,[26,74] there is an additional defect in the apical trabecular septum, the conduction tissue could pass through the bar of muscle separating the two defects. If the usual defect undergoes spontaneous closure, the bundle may run through the roof of the remaining ventricular septal defect.

When this ventricular pattern is associated with absence of the right AV connection[68] the AV node is as described for classic tricuspid atresia as above. The intraventricular portion is as described immediately above for double inlet with an extensive course of the nonbranching bundle.

When the left AV valve is absent, the right AV valve provides a separation of the regular and anterior nodes. The regular node makes no contact with the anteriorly displaced septum, therefore the anterolateral node gives rise to the penetrating bundle, which takes the same extensive intraventricular course described for double inlet.

When there is straddling of the left AV valve in this ventricular arrangement, the node and conduction tissues are similar to double inlet described above, regardless of the degree of straddling.[68] To my knowledge, the conduction system in straddling right valve has not been described.

Dominant Right Ventricle. In this arrangement the nondominant left ventricle is located to the right. The posterior extent of the ventricular septum reaches the crux. Since the ventricular architecture is left-hand, one might expect an anterior AV node. On the other hand, the septum does reach the crux, and when this occurs in double-inlet right ventricle with normally related ventricles, the AV node is in regular position. The conduction tissue in a single heart with this morphology has been described.[75] In this heart both anterior and regular AV nodes were found placed close together and connected by a "sling" of conduction tissue passing through the fibrous annulus but not related to the trabecular septum. The nonbranching bundle descended to a free running trabecula in the right ventricle, the trabecular septal tissue itself being devoid of conduction tissue. The trabecula was felt to represent the septomarginal trabecula of the normal right ventricle.

The anatomy of the conduction tissue in hearts with left-hand architecture and biventricular AV connection with straddling right AV valve has been described. In these hearts both regular and anterior nodes were present, connected by a "sling" of conduction tissue.

Two hearts with left-hand architecture, dominant right ventricle and absent right AV connection and straddling left AV valve have been described.[68] A node was present in the floor of the blindly ending right atrium, from which an anterior bundle penetrated and ran onto the anterior margin of the septal defect. From there, a sling of conduction tissue ran along the septal crest, ascending to penetrate the annulus and form a second node in the posterior wall of the left atrium. Absence of the left AV connection has not been reported with this ventricular architecture.

Indeterminate Ventricular Morphology

In hearts in this group there is a second ventricle present and therefore no apical septal structure. These hearts would be expected to have an anterior node and the bundle should simply run down the parietal wall of the ventricle at the acute margin of the AV junction.[76] The presence of a prominent septomarginal trabecula has been seen to modify this arrangement.[77] In one heart this trabecula that carried the bundle extended to the underside of the atrium. The node was in the atrial septum and the bundle penetrated at the apex of the triangle of Koch. In another case the trabecula ran to the underside of the ventriculoinfundibular fold.

In hearts with biventricular AV connection and a large ventricular septal defect, the AV node is usually normally placed and the bundle runs in a remnant of inlet septum on the posterior wall of the ventricular mass[78,79] Becker et al.[56] reported a case in which the posterior ridge became diminutive as it approached the crux. One anterior prominent marginal trabeculation was found to carry the bundle from an anomalous anterolateral node.

General rules for prediction of location of conduction tissue are presented in Table 74–3.

EMBRYOLOGY

The embryology of the normal heart is incompletely understood. Numerous terminologies have been used to describe the various

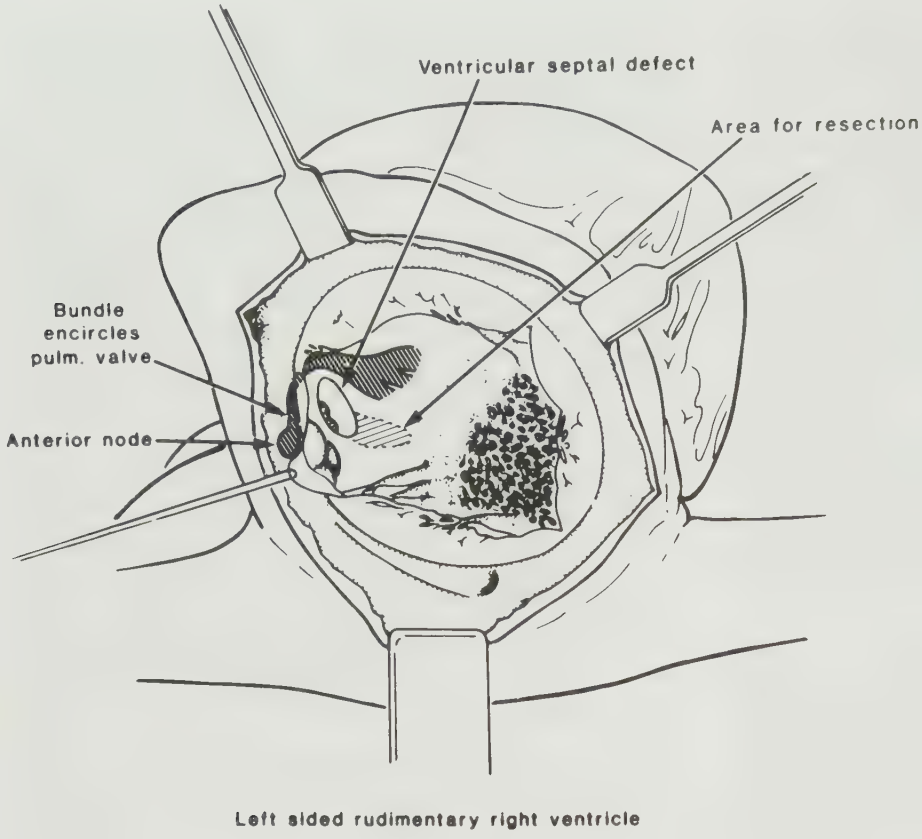

Fig. 74–9. View of the conduction axis and area of safe resection to enlarge the ventricular septal defect in dominant left ventricle with left-hand architecture, seen through right atriotomy and right atrioventricular valve. (From Anderson, R.H., et al.: Disposition of the conduction tissues. *In* Double Inlet Ventricle. Edited by R.H. Anderson, G. Crupi, and L. Parenzan. Tunbridge Wells, Kent, Castle House Publications, 1987.)

Table 74–3. Rules for the Prediction of Conduction Tissue

Is there a septum in the ventricular mass?
No —solitary indeterminate ventricle
There will be an anterolateral node (unless trabeculation joins atrial septum)
Yes
Does the septum extend to the crux?
No —double-inlet left ventricle
There will be an anterolateral node
Yes—but deviated to produce double-inlet right-ventricle conduction tissue determined by ventricular topology
Right-hand pattern—node in triangle of Koch
Left-hand pattern —anterior node or sling
Yes—but hypoplastic apical structure, huge ventricular septal defect
Inlet septal remnant—node in triangle of Koch
No inlet septum —anterior node
Left-hand topology —anticipate anterior node

From Anderson, R.H., et al.: Disposition of the conduction tissues. *In* Double Inlet Ventricle. Edited by R.H. Anderson, G. Crupi, and L. Parenzan. Tunbridge Wells, Kent, Castle House Publications, 1987.

structures and structural changes. Until direct observation of the development of normal and abnormal human hearts is possible, comments about the development processes will remain somewhat speculative.

The ventricular mass is first considered. The right- or left-handedness of the ventricular pattern has been presumed to be a consequence of the direction of the acute bend in the heart during looping. If the convex margin is directed to the right (d-loop) the right-handed pattern will result, if to the left (l-loop) the left-handed pattern. Even this generally accepted speculation has been doubted.[80]

Dominant Left Ventricle

The hearts with double inlet via a common valve to a dominant left ventricle resemble the embryonic heart[81,82] at Streeter's stage XIII.[83–85] At this stage, the partially divided atrial mass communicates via an undivided AV valve with the descending limb of the bulboventricular loop variously called the primitive ventricle,[5,86] left ventricle,[81] inlet segment,[87] or proampulla.[88,89] There is controversy as to the embryonic derivation of the left and right ventricles in the normal heart. De la Cruz and Miller,[81] based on Streeter, state that the primitive ventricle (descending limb) gives rise to the sinus of the definitive left ventricle only and that the bulbus cordis gives rise to the sinus of the right ventricle and to the outflow portions of both right and left ventricles.

Lev[5] quotes Pernkopf and Wirtinger[88] in stating that the descending limb, or proampulla, gives rise to the sinuses of both right and left ventricles while the ascending limb, metampulla or bulbus, gives rise to part of the sinus of the right ventricle and to

the outlet portion, conus, of both ventricles. The work of Wenink[87] seems to support the latter opinion. Van Praagh et al. reexamined the work of Pernkopf and Wirtinger and concluded that the difference is a misinterpretation of terms, i.e., this work in fact agrees with Streeter's concerning the derivation of the ventricles. If De la Cruz and Miller are correct, then the dominant ventricle is the primitive left ventricle and the nondominant chamber is the right ventricle. If Pernkopf and Wirtinger (as interpreted by Lev) are correct, then the dominant ventricle is not simply the primitive left ventricle but also contains a portion of the right sinus.

The nature of the structure separating the dominant and nondominant chambers of these hearts has been debated. De la Cruz and Miller suggested that it is the malaligned posterior septum, assuming an anterior position as a consequence of failure of migration of the right atrioventricular canal to the bulbus. They quote as evidence in support of this concept the fact that in some cases the right valve straddles the anterior septum. These hearts with straddling are thought to represent intermediate steps in the migration of the right AV orifice from left ventricle to the bulbus.

Anderson et al.[86] examined several pathologic specimens with double-chamber right ventricle in which both anterior and posterior septa were felt to be present and concluded that one could not possibly be formed by realignment of the other. Based on these hearts they concluded that the anterior septum is a persistent right bulboventricular ridge.

Van Praagh et al.[1] concluded that it is the displaced ventricular septum that separates the two chambers. They speculated that, when the right ventricle fails to evaginate or outpouch from the metampulla, then expansive growth fails to carry the ventricular septum leftward to underlie the atrial septum and separate the developing AV valves.

Van Mierop[90] believes that the structure separating the two chambers is homologous with the major part of the normal ventricular septum and that it is displaced to the right. This, he says, occurs when the AV canal is abnormally oriented, becoming "trapped" to the left of the bulboventricular septum. With further expansion of the right AV ostium, the septum is pushed rightward and blends with the trabecula septomarginalis, while the posterior medial muscle bundle[5] cannot blend with the posterior portion of the muscular septum. This posterior ridge formed concomitant with partitioning of the AV canal does retain its normal relationship with the atrial septum, crux cordis, and the posterior descending artery.

Dominant Right Ventricle

Munoz-Castellanos et al.[91] described two cases of double inlet to a dominant right ventricle. The two ventricles communicated via a basilar ventricular septal defect, and there was straddling and overriding of the AV valve. They recognized this defect to be much more rare than double-inlet left ventricle. This, they supposed, was because double-inlet left ventricle represented the persistence of a normal developmental stage while double inlet right ventricle represented an alteration in normal development of the AV connections. They postulated that double-inlet right ventricle originates from a precocious and prolonged widening of the AV canal from left to right. This process, beginning at Streeter's Horizon XIII and normally continuing through Horizon XV, does not stop at the time when the interatrial septal complex is aligned with the interventricular septum, but is continued exaggeratedly to the right.[92] The usual underdevelopment of the left ventricle in these hearts is presumed secondary to the altered hemodynamics resulting from the displacement of the AV canal. Other authors[87,93,94] deny the rightward shift of the AV canal as a process in normal development. Dor and Corone[93] would say the ventricular septum shifts to the left. Wenink[87] contends the normal septation of the inlet segment results in the right portion of the AV canal being related to the right portion of the inlet segment of the ventricular mass from the earliest appearance of the inlet septum. Using this concept one might postulate that double-inlet right ventricle results from an abnormal partition of the inlet segment together with failure of the left portion of the inlet segment to enlarge.

The mode of atrioventricular connection seems determined by events taking place in the septation of the AV canal. If the endocardial cushions develop normally, then the canal will be divided, resulting in double inlet. A later abnormality may result in one of these orifices being imperforate. If the partitioning fails to occur, a common AV valve results. If partitioning occurs asymmetrically, stenosis of one orifice will result. Absence of an atrioventricular connection is postulated to occur when the endocardial cushions develop at the periphery of the atrioventricular orifice. The atrial septal structures then align with the cushions (Fig. 74–10).

The presence of overriding is a consequence of a malalignment between the structures dividing the atria/atrioventricular canal and the developing ventricular septum. The tensor apparatus develops much later as a result of undermining of the ventricular myocardium.[87] This later process of ventricular undermining then is responsible for the varying degrees of straddling.

INCIDENCE

Since this chapter deals with a group of hearts and not a single anatomic diagnosis, and since many different names have been used it is difficult to state the incidence precisely. Kidd[95] has reported finding a single ventricle in 1.1% of children with congenital heart defects. Thies et al.[40] reported 218 local cases accumulated over a 20-year period at University of Alabama Birmingham. Macartney et al.[62] found 42 cases in a 5-year period. While most patients have no chromosomal abnormality, case reports[96] documented occasional associations. Occurrence in siblings has been reported.[43]

The relative incidence of the different ventricular morphologies within this group of hearts is also difficult to obtain. Hearts with a dominant right ventricle have only recently been recognized and identified as a part of this group. In the series of Van Praagh et al.[4] hearts with double inlet to a right ventricular chamber were only included if a second small chamber was not present. However, some may have had tiny left ventricles, since microscopic sectioning is sometimes required to identify these chambers. This series of 60 hearts contained 47 (78%) with a dominant left ventricle, which Van Praagh et al. called type A; only 3 hearts (5%) with dominant right ventricle, which they called type B; 6 hearts (10%) with a single chamber of indeterminate morphology, which they called type D; and 4 hearts (7%) with absent or rudimentary development of the sinus portion of the ventricular septum, which they called type C.

In a second series Van Praagh et al.[1] reported an additional 31

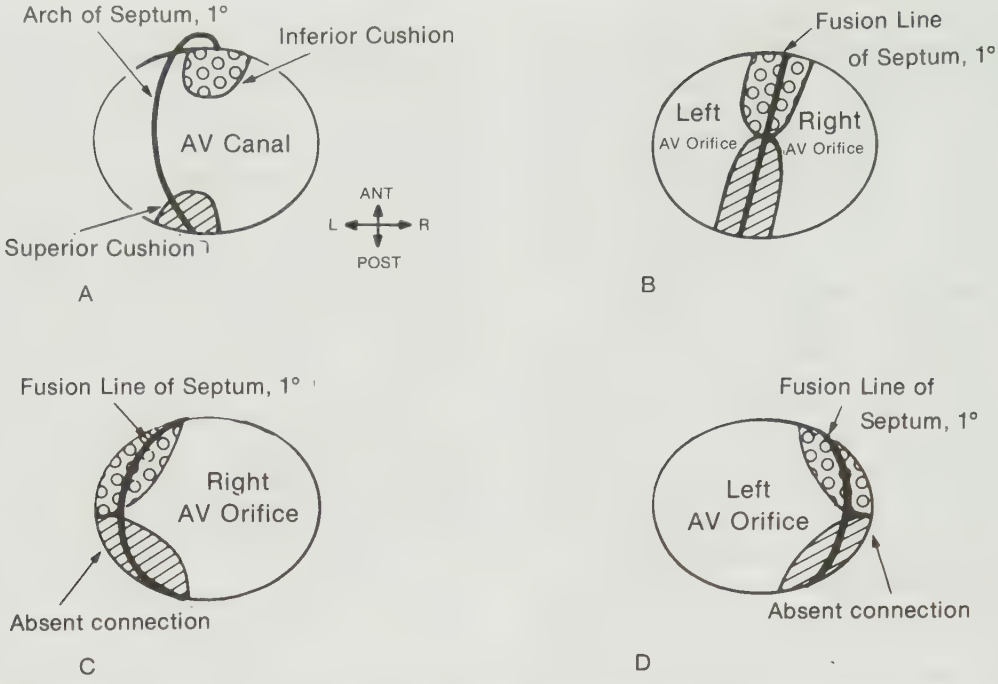

Fig. 74–10. Proposed mechanism of producing A) normal and abnormal development, B) double inlet, C) absent left atrioventricular connection, or D) absent right atrioventricular connection. (From Becker, A.E., Wilkinson, J.L., and Anderson, R.H.: Atrioventricular conduction tissues: A guide in understanding the morphogenesis of the univentricular heart. *In* Etiology and Morphogenesis of Congenital Heart Disease. Edited by R. Van Praagh and A. Takao. Mount Kisco, NY, Futura, 1980.

cases, of which 23 (74%) had dominant left ventricle—14 (45%) with l-loop and 9 (29%) with d-loop. Of the 8 (26%) cases with dominant right ventricle (they allowed a tiny left in this series), 6 (20%) had d-loop and 2 (6%) had l-loop.

In an angiographic study,[44] in which hearts with absence of one AV connection were included, 36 of 54 patients had dominant left ventricle and 13 dominant right while 5 were felt to have indeterminate morphology. Of the hearts with dominant-left architecture, the nondominant right was anterior and rightward in 17, leftward in 12 and directly anterior in 6. Of the 13 patients with a dominant right ventricle, a second ventricle of left ventricular type could be seen posteriorly in 8, though it is not mentioned how many were right- or left-sided.

The most detailed information on pathologic specimens is reported by Anderson et al.[97] This series of hearts was obtained from several institutions and included hearts with one absent AV connection as well as hearts with double inlet. Of 237 hearts, 140 had dominant left ventricle, 34 dominant right ventricle, and 41 indeterminate morphology. Of these hearts, 87 had a dominant left ventricle and absent right AV connection, and thus would be listed in other series as classic tricuspid atresia. While the right- or left-handedness of the ventricular mass is not listed specifically, this can be inferred from the position of the nondominant chamber (Table 74–4). The details concerning atrial situs (Table 74–5), nature of the nondominant ventricle (Table 74–6), mode of atrioventricular connection (Table 74–7), and arterial connections (Table 74–8) are listed.

Of interest, approximately one quarter of the hearts with a second chamber in the ventricular mass exhibited straddling of one of the atrioventricular valves or of part of a common valve. In the majority the straddling was said to be minimal while in some hearts it approached 50%. In a surgical series Stefanelli et al.[41] reported an incidence of straddling of 13%.

The detailed information from the surgical series at University

Table 74–4. Position of Rudimentary Chamber

	Right-sided	*Directly Anterior*	*Left-sided*
Left-ventricle–type univentricular heart			
Double inlet	71	42	37
Absent right connection	83	—	4
Absent left connection	1	—	9
Right-ventricle–type univentricular heart			
Double inlet	3	—	22
Absent right connection	1	—	5
Absent left connection	—	—	3

From Anderson, R.H., et al.: Ventricular morphology in the univentricular heart. Herz, *4*:184, 1979.

Table 74–5. Atrial Situs

	Solitus	*Inversus*	*Ambiguus*	*Total*
Left ventricular type	228	1	8	237
Right ventricular type	22	—	12	34
Indeterminate type	22	2	17	41
Total	272	3	37	312

From Anderson, R.H., et al.: Ventricular morphology in the univentricular heart. Herz, *4*:184, 1979.

of Alabama Birmingham includes cases with AV valve atresia. The information is listed by the type of ventricular architecture and dominant ventricle. (Tables 74–9, 74–10, and 74–11). Associated cardiac lesions, common in all series, are detailed in Table 74–12. Coarctatation and interruption are not listed in this table. In a series of patients presenting in the first year of life, these lesions were found in 16%. Other associated anomalies found in this series are listed in Table 74–13.

The incidence of dextrocardia is not given in the series of Anderson et al.,[97] but in Van Praagh and colleagues' series[4] 11 of 60 hearts exhibited dextrocardia, 7 with dominant left ventricle (type A), 2 with indeterminate ventricle (type D), and 2 with large ventricular septal defect and biventricular connection (type C). In a series of hearts with dextrocardia[98] 10 of the 16 hearts with situs solitus, 2 of the 11 with situs inversus, and 2 of the 6 with situs ambiguus were said to have univentricular hearts.

Of the 43 cases reviewed by Lev et al.,[5] 7 had dextrocardia. Abnormalities of atrial situs associated with abnormalities of systemic and pulmonary venous connections, multiple or absent spleens and common AV valves are more commonly seen with dominant right ventricle, and ventricles of indeterminate morphology, though cases with dominant left ventricle are seen.[97,99]

CLINICAL FINDINGS

Most patients present early in life with cyanosis due to inadequate pulmonary blood flow, or congestive heart failure if pulmonary artery blood flow is unobstructed or if pulmonary venous return is obstructed. A few children who are congenitally optimally palliated will present later in childhood with asymptomatic murmur and mild clinical cyanosis.[100] Decreasing exercise tolerance or increasing cyanosis may bring them to the attention of a cardiologist.[101] A few neonates with left outflow obstruction will have onset of poor perfusion when the ductus closes in the first few days of life. Aortic atresia, through rare, has been described.[1] From a series of all patients with single ventricle treated surgically,[41] 25% of the patients came to their first operation by 3 months of age, 50% by 22 months of age, and 75% by 7 years of age.

Table 74–6. Type of Rudimentary Chamber

	Outlet Chamber	*Trabecular Pouch*
Right ventricular type	228	9
Left ventricular type	8	26
Total	236	35

From Anderson, R.H., et al.: Ventricular morphology in the univentricular heart. Herz, *4*:184, 1979.

Pulmonary stenosis was present in 64% and atresia in 5% of the cases reported by Stefanelli et al.[41] When present, this usually determines the clinical presentation. Patients with pulmonary atresia or severe pulmonary stenosis may present with profound cyanosis and acidosis when the ductus spontaneously closes in the first few days of life. In earlier series, these patients probably died without coming to surgery. More recently, the widespread availability of prostaglandin E_1, used to reopen the ductus, has allowed more of these patients to survive to operation. In addition, the patients coming to operation now are usually not acidotic or severely cyanotic.

If the pulmonary blood flow is restricted by pulmonary stenosis but adequate to maintain adequate systemic oxygenation, then no palliative procedure is required. Pulmonary blood flow may become inadequate with growth as the fixed pulmonary valvular ostial size fails to grow at the same pace as the rest of the patient. Obstruction to pulmonary blood flow may also be subvalvar, caused by a restrictive ventricular septal defect or hypertrophy of subpulmonary muscle. Either of these types of subpulmonary stenosis may exhibit progressive obstruction and complete occlusion of the pulmonary outflow.[52] Much less commonly, subpulmonic obstruction may be due to redundant fibrous tissue arising in association with one of the AV valves.

It should be pointed out that while the degree of cyanosis is usually determined by the amount of pulmonary blood flow, in patients with intact atrial septum and significant streaming of flow within the ventricles cyanosis may be less (favorable streaming) or greater (unfavorable streaming) than expected if full mixing were taking place.[102]

Patients without pulmonary stenosis may present with a murmur or gallop in the first few days of life, but clinical symptoms do not usually become apparent until three to six weeks of age, when the fall in pulmonary vascular resistance allows excessive pulmonary blood flow. The findings at that time will be congestive heart failure with tachypnea, subcostal retraction, poor feeding, hepatamegaly, and splenomegaly. Digitalis and diuretics allow shortterm improvement but palliative or two-stage "corrective" surgery[103] is required for longterm survival.

In patients with left AV valve atresia or severe stenosis and nearly intact interatrial septum, symptoms of pulmonary venous hypertension may develop as arteriolar resistance falls and pulmonary blood flow increases. This problem may also become apparent following placement of a systemic-to-pulmonary-artery shunt. Ideally, the restriction to pulmonary venous return should be recognized by echocardiography and aggressively treated by balloon atrial septostomy in the neonatal period. If recognized later, balloon atrial septostomy is less likely to be successful and either blade septostomy or Blalock–Hanlon atrial septectomy will be required. It should be pointed out that obstructed total anomalous pulmonary venous connection occurs, though rarely, with a single ventricle and that symptoms in this form of obstruction may also be provoked by a successful shunting procedure.[104]

Rarely, a patient with severe AV valve insufficiency (usually of a common AV valve) may present with severe intractable heart failure. Though valve replacement has been accomplished in older patients, the outlook for a neonate with severe AV valve insufficiency is grim.

Subaortic obstruction may appear in the first few days of life.[4] If present, the fetal circulation pattern has usually been abnormal

Table 74–7. Hearts Studied

Left ventricular type			
With double inlet			(140 hearts)
Two atrioventricular valves		129	
Straddling right valve	17		
Straddling left valve	13		
Imperforate right valve	2		
Imperforate left valve	1		
Common atrioventricular valve		11	
Straddling valve	2		
With absent right AV connection			(87 hearts)
Valve committed to main chamber		86	
Straddling left valve		1	
With absent left AV connection			(10 hearts)
All committed to main chamber			
Right ventricular type			
With double inlet			(25 hearts)
Two atrioventricular valves		6	
Straddling left valve	1		
Straddling right valve	1		
Common atrioventricular valve		19	
Straddling valve	1		
With absent right AV connection			(6 hearts)
Valve committed to main chamber		2	
Valve straddling septum		4	
With absent left AV connection			(3 hearts)
Valve committed to main chamber		2	
Valve straddling septum		1	
Indeterminate type			(40 hearts)
With double inlet			
Two atrioventricular valves		17	
Common atrioventricular valve		23	
With absent left AV connection			(1 heart)

From Anderson, R.H., et al.: Ventricular morphology in the univentricular heart. Herz, *4*:184, 1979.

Table 74–8. Arterial Connections

	Concordant	*Discordant*	*DOMC*	*DOOC*	*Single Outlet*
Left ventricular type					
Double inlet	21	94	7	6	12
Absent right connection	66	17	2	1	1
Absent left connection	1	9	—	—	—
Right ventricular type					
Double inlet	8	—	10	—	7
Absent right connection	—	—	5	—	1
Absent left connection	—	—	3	—	1
Indeterminate type					
Double inlet			34		6
Absent left connection			1		—

From Anderson, R.H., et al.: Ventricular morphology in the univentricular heart. Herz, *4*:184, 1979
DOMC = double outlet main chamber
DOOC = double outlet from outlet chamber

Table 74–9. Ventricular Architectural Pattern and Dominance and the Status of the Pulmonary Outflow Tract in Surgical Cases of Univentricular AV Connection (UAB; 1967–1982). Cases with Classic Tricuspid Atresia are Excluded

Ventricular Architectural Pattern	*Main (Dominant) Ventricular Chamber*	*Number of Cases*	*Pulmonary Outflow*		
			Stenosis	*Atresia*	*Open*
Solitary ventricle	NA	23	19	3	1
Two ventricles		37	25	2	10
Right-handed (d-loop)	LV	24	15	2	7
	RV	13	10	0	3
Left-handed (l-loop)		50	27	0	23
	LV	47	24	0	0
	RV	3	3	0	0
Undetermined		4	2	1	1
	LV	3	2	1	0
	RV	1	0	0	1
Total		114	73 (64%)	6 (5%)	35 (31%)

Note: "Open" indicates that no pulmonary stenosis is present. The (%) refers to percentage of 114. Not included are two patients with atrial situs inversus.
NA = not applicable; LV = left ventricle; RV = right ventricle.
From Kirklin J.W., and Barratt-Boyes, B.G.: *Cardiac Surgery.* New York, Wiley, 1983.

and there is often a reduction in the size of the ascending aorta and severe coarctation or interruption of the aortic arch. Such patients depend on the patent ductus arteriosus for systemic blood flow. When the ductus undergoes spontaneous (or unfortunate surgical or indomethacin closure) in a child with unrecognized heart disease inadequate perfusion leads to profound acidosis and death. Administration of prostaglandin E_1 may reopen the ductus if spontaneously closed. The long-term surgical outlook for such patients is grim (see section on palliative surgery).

DIAGNOSIS

The physical findings will depend more on the physiology than on the particular ventricular morphology or mode of atrioventricular connection. With pulmonary stenosis or atresia, cyanosis will be more remarkable. With stenosis there will be a harsh ejection murmur at the base of the heart. If subpulmonary stenosis progresses, the murmur may become quieter and shorter and cyanosis may deepen. If there is obstruction to pulmonary venous return, the ejection murmur of pulmonic stenosis may be minimized. With pulmonary atresia there will be no harsh ejection murmur, but a continuous murmur from ductal patency may be heard. The second heart sound will be single. If the aorta is anterior, the second heart sound may be loud and the component due to the pulmonary valve, if present, may be difficult to appreciate.

If there is no pulmonary stenosis and a nonrestrictive ventricular septal defect, there will usually be a nonspecific systolic murmur

Table 74–10. Ventricular Architectural Pattern and Dominance and the Nature of the Univentricular AV Connection in Surgical Cases of Univentricular AV Connection (UAB; 1967–July 1982)

Ventricular Architectural Pattern	*Main (Dominant) Ventricular Chamber*	*Number of Cases*	*AV Valves*			
			Common	*Double Inlet*	*Left-Sided AV Valve Atresia*	*Right-Sided AV Valve Atresia*
Solitary ventricle	NA	23 (20%)	13	10	0	0
Two ventricles						
Right-handed (d-loop)		37 + 89	6	24	6	1 + 89
	LV	24	4	19	1	0 + 89
	RV	13	2	5	5	1
Left-handed (l-loop)		50	0	43	6	1
	LV	47	0	41	6	0
	RV	3	0	2	0	1
Undetermined		4	1	2	1	0
	LV	3	1	2	0	
	RV	1	0	0	1	
Total		114 + 89	20 (18%)	79 (69%)	13 (11%)	2 + 89 (2%)

Note: The underlined numbers refer to classic tricuspid atresia. The (%) refers to the percentage of 114. Not included are the two patients with atrial situs inversus, both of whom had two ventricles in d-loop. One of these had a dominant left ventricle with common AV valve, ventriculoarterial concordant connection, and pulmonary stenosis; the other had dominant right ventricle, common AV valve, double-outlet right ventricle, and pulmonary stenosis.
NA = not applicable; LV = left ventricle; RV = right ventricle.
From Kirklin, J.W., and Barratt-Boyes, B.G.: *Cardiac Surgery.* New York, Wiley, 1983.

Table 74–11. Ventricular Architectural Pattern and Dominance and the Nature of the Ventriculoarterial Connection in Surgical Cases of Univentricular AV Connection (UAB; 1967–July 1982)

Ventricular Architectural Pattern	*Main (Dominant) Ventricular Chamber*	*Number of Cases*	*Ventriculoarterial Connection*		
			Concordant	*Discordant*	*Double Inlet*
Solitary ventricle	NA	23	NA	NA	23
Two ventricles					
Right-handed (d-loop)		37	12	11	14
	LV	24	12	10	2
	RV	13	0	1	12
Left-handed (l-loop)		50	0	47	3
	LV	47	0	46	1
	RV	3	0	1	2
Undetermined		4	1	1	2
	LV	3	1	0	2
	RV	1	0	1	0
Total		114	13	59	42

Note: There were no patients with a common arterial trunk. Not included are the two patients with atrial situs inversus (see legend to Table 74–9).
NA = not applicable; LV = left ventricle; RV = right ventricle.
From Kirklin, J.W., and Barratt-Boyes, B.G.: *Cardiac Surgery.* New York, Wiley, 1983.

Table 74–12. Associated Cardiac Anomalies in Surgical Cases of Univentricular AV Connection, According to Atrial Situs (University of Alabama, Birmingham; 1967– July 1982; n = 116)

Associated Cardiac Anomaly	*Number**			
	Situs Solitus (n = 101)	*Situs Inversus (n = 2)*	*Situs Ambiguus (n = 12)*	*Total (n = 116)*
Straddling AV valves				
Straddling + overriding	6	0	0	6
Straddling only	8	0	0	8
Overriding only	1	0	0	1
ASD—fossa ovalis type	23	0	1	24
ASD—sinus venosus type	1	0	0	1
ASD—common atrium	1	0	1	2
PDA	5	2	10	17
TAPVC	15	0	4	19
LSVC	7	0	2	3
Other anomalies of venous return	5	2	3	12
Multiple ventricular septal defects	9	2	11	18
Dextrocardia	3	0	0	9
Over–Under ventricle: right ventricle superior	2	0	0	2
Others	9	0	1	10

*One patient has unknown situs without other associated cardiac anomaly.
ASD = atrial septal defect; PDA = patent ductus arteriosus; TAPVC = total anomalous pulmonary venous connection; LSVC = left superior vena cava.
From Kirklin, J.W., and Barratt-Boyes, B.G.: *Cardiac Surgery.* New York, Wiley, 1983.

Table 74–13. Major Associated Cardiovascular Lesions

Lesion	*Number*	*Percentage*
Coarctation/interrupted aorta	27	16
Aortic valve stenosis	6	4
Aortic atresia	3	2
Subaortic obstruction	8	5
Pulmonary stenosis	50	29
Pulmonary atresia	37	22
Pulmonary artery stenosis interruption	7	4
Extracardiac total anomalous pulmonary venous connection	18	10
AV valve stenosis/imperforate	13	8

Deanfield, J.E., et al.: Factors influencing presentation and prognosis. *In* Double Inlet Ventricle. Edited by R.H. Anderson, G. Crupi, and L. Parenzan. Tunbridge Wells, Kent, Castle House Publications, 1987.

and a diastolic flow rumble or gallop. If there is a subaortic stenosis,[105] there will usually be a harsh murmur, but there may be important narrowing of the ventricular septal defect without a loud murmur. If there is associated coarctation and the ductus has closed, there will be decreased femoral pulses. If the ductus is still patent, there may be brisk lower-extremity pulses even in the presence of severe coarctation or interruption.

CHEST ROENTGENOGRAPHY

The findings on chest roentgenography are dependent on the degree of pulmonary outflow obstruction. With moderately restricted pulmonary blood flow there will generally be a near-normal heart size and pulmonary vascular markings. When pulmonary blood flow is severely obstructed, the pulmonary vascular markings will be decreased. When there is mild or no pulmonary stenosis, there will be cardiomegaly with increased pulmonary vascular markings. The sidedness of the stomach bubble may provide information about the abdominal situs. If atrial isomerism is suspected, high kilovolt films or tomograms[106] may allow evaluation of bronchial anatomy. If pulmonary venous return is severely obstructed in the setting of total anomalous pulmonary venous return or mitral atresia/stenosis, the lung fields will assume a reticular pattern and the heart size will be normal to mildly increased. In patients with dominant left ventricle and left-hand architecture a notch can sometimes be seen on the left heart border marking the site of the small right ventricle. In these patients the left heart border will often have a straight appearance, as seen in patients with congenitally corrected transposition.

ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiographic findings are quite variable.[107,108] There is generally sinus rhythm and the PR interval is generally normal, though first-degree heart block was present in 30% of the patients reported by Gillette.[109] None of the patients with first-degree heart block progressed to complete heart block during followup. Seven patients had serious supraventricular tachydysrhythmias including atrial flutter in three. Four patients had Wolff–Parkinson–White syndrome and one Lown-Ganong–Levine syndrome. Congenital complete heart block will be present in a few patients: 3 of 116 surgical patients[41] and 5 of 105 patients reported by Gillette.[109] Heart block did not develop in any patient followed without surgery by Moodie et al.[101] Supraventricular tachycardia was documented in three of their patients and in both the surgically palliated[110] and nonpalliated series, dysrhythmia was listed as a cause of death. Sudden death was seen in these patients and in patients who underwent a septation procedure.[41,111]

Efforts to relate the vectorcardiogram or the sidedness of hypertrophy on scalar electrocardiography with the morphologic type of the ventricular mass have been disappointing.[107,108] A number of patients will have no evidence of ventricular hypertrophy. The frontal plane QRS axis will often be normal but may be found in the upper quadrants. The P-wave axis may be abnormal, especially when atrial isomerism and bilateral left-sidedness are present.

Electrophysiologic testing has been reported both in the catheterization laboratory[109,112] and in the operating room.[79,113] The intraoperative studies confirmed expected sites of specialized conduction tissue. The sites of first degree AV block were found to be variable and multiple sites of atrioventricular delay could be found in individual patients.

TWO-DIMENSIONAL AND DOPPLER ECHOCARDIOGRAPHY

M-mode echocardiography is capable of demonstrating the presence of one large chamber within the ventricular mass. Usually the number and location of AV valves can also be discerned.[114] The annulus size and general relative location of the semilunar valves can be worked out by an experienced M-mode operator.[115–120]

Two-dimensional echocardiography greatly reduced the time required to obtain this information and provided much more secure information about spatial relationships.[121–123] Clues to the situs are obtained from the systemic venous anatomy.[124] The type and mode of AV connection are well seen.[125] Straddling and overriding of AV valves may be assessed more accurately by echocardiography than by angiography.[58] The presence and size of atrial septal defects can be evaluated. When an outlet chamber is present, the chamber and the size and location of the ventricular septal defect can usually be seen.[126] The small posterior left ventricle associated with a dominant right ventricle may be seen, or it may be too small to be seen. The differentiation of the morphologic type of the main ventricle may often be inferred from the associated nondominant chamber, but the apical trabecular pattern of the ventricles is not reliably discernible with current techniques.[123,127]

The ventriculoarterial connections and spatial relationships can usually be well seen, as can the presence of subvalvar or valvar stenosis. This usually requires both parasternal long- and short-axis views. From the suprasternal notch the sidedness of the arch and location of the patent ductus, if present, can be visualized. In cross section one can usually visualize the bifurcation of the pulmonary arteries. The systemic venous return can also be seen from this view, often showing bilateral superior caval veins. Deep in relation to the pulmonary arteries, the pulmonary veins can usually be seen entering the left atrium or forming a confluence behind the left atrium. In the presence of total anomalous pulmonary venous return, multiple suprasternal and subcostal veins

will usually demonstrate the location of the connection between the pulmonary venous confluence and the systemic veins.

Pulsed, range-gated Doppler sampling allows detection of flow in the ductus if present and allows differentiation of venous from arterial structures in complicated cases.[128] Insufficiency of AV valves can be detected and semiquantitated. If pulmonary stenosis is severe, Doppler interrogation will allow differentiation of stenosis from atresia.

Color flow mapping is quite useful, providing similar information to that obtained by pulsed, range-gated Doppler but providing much more information in each frame. The duration of the examination is reduced, and unsuspected abnormal flows may be detected.

Continuous-wave Doppler combined with imaging is of great utility, allowing quantitation of gradients across valves, ventricular septal defect, pulmonary venous connections, and coarctations. The combination of continuous wave, two-dimensional structural, and color flow mapping obtained simultaneously is very important in these hearts with highly variable structural anatomy and many high-velocity jets.

Usually, the structure and physiology are well demonstrated by these noninvasive techniques and catheterization can be directed to obtaining information not available by echocardiography. The fluoroscopy time required may be reduced because of echocardiography, and the angled views can be planned according to the form of the individual heart and the information required. In many cases, catheterization can be safely postponed and done on a larger, less fragile child.

Quantitation of two-dimensional images has been used to assess ventricular function in patients with double inlet.[129] The authors found global indices of ventricular function to be remarkably normal. End diastolic volumes were large, as might be expected. Wall-motion abnormalities were common, although there was no consistent pattern, timing, or location. Wall-motion abnormalities were unrelated to age, hematocrit, or previous palliative surgery. This observation raises questions about the usefulness of M-mode measurements of shortening fraction in these patients. The relatively normal function contrasts with reports concerning tricuspid atresia[130,131] and with angiographic studies[132] in single ventricle.

OTHER IMAGING MODALITIES

Magnetic resonance imaging presently[133] provides little information not obtained more quickly, precisely, and cheaply by two-dimensional and Doppler echocardiography. This modality may be useful in older patients with poor windows for echocardiography. Imaging of deep, static structures, such as systemic and pulmonary veins, may be improved using magnetic resonance imaging. Coarctation may be evaluated, and these images may be especially helpful in following patients postoperatively.

Radioisotope techniques may be used to assess ejection fraction. However, in children we usually evaluate ventricular performance with echocardiography,[129] to avoid radiation exposure. The advantage to isotope techniques is that no assumption about the geometry of the ventricle is required. These techniques have been applied to patients with tricuspid atresia[130] and to those with single ventricle.[134]

CARDIAC CATHETERIZATION

Cardiac catheterization should be planned on the basis of information obtained by two-dimensional and Doppler echocardiography. The timing of the catheterization may be dictated by the need for intervention in the newborn period, when balloon atrial septostomy, shunting, or banding is necessary.

At catheterization the systemic venous anatomy should be explored. Usually the presence of bilateral superior vena cavae is demonstrated echocardiographically, but it is helpful to document the catheter course into each. When the venous drainage from the lower half of the body enters the heart via an azygos vein continuation to the superior vena cava, this is usually strongly suspected from echocardiography. In the catheterization laboratory, the catheter in the vein behind the heart may appear to be within the heart. An inability to bring the catheter in an anterior direction, and identical saturations below, "within," and above the heart should suggest the diagnosis. A small injection of contrast material by hand will usually clarify the situation. A deflector wire will help in making the curve anteriorly and downward into the heart. In newborns, especially, this tight curve makes further manipulation of the catheter within the heart more difficult. Careful measurement of oxygen saturation will help document anomalous connection of the pulmonary veins if present. When the site of anastomosis is seen echocardiographically, it may be possible to pass the catheter into the pulmonary venous confluence. Pressure measurements and angiography here will allow an assessment of the presence and degree of obstruction.

Within the heart both atria can commonly be entered, but an intact atrial septum may prevent easy passage of a catheter into the pulmonary venous atrium. If the AV valve draining the pulmonary venous atrium is suspected to be stenotic, transseptal technique may be indicated.

The dominant chamber can almost always be entered. The nondominant chamber can also frequently be entered and this should be done when possible to document any pressure gradient across the ventricular septal defect. If echocardiography has suggested a small ventricular septal defect, then measurements should be taken quickly. Angiography, if necessary, should be performed, and the catheter removed. In the setting of a restrictive ventricular septal defect, the catheter may be large enough to reduce significantly the flow through the ventricular septal defect into the aorta or pulmonary artery.

Both the aorta and pulmonary arteries can often be entered.[62] There may be streaming of arterial and venous blood within the heart so that pulmonary and aortic oxygen saturations may differ significantly.[135–138] When there is a large atrial septal defect, total anomalous pulmonary venous connection, atresia of one AV valve, or pulmonary atresia, total mixing of systemic and venous blood generally occurs (36% of the patients in Macartney et al.'s report[135]). Streaming was favorable with aortic saturation higher than in the pulmonary artery in 52%. Unfavorable streaming occurred in 12%. In one patient an aortic saturation of 97% (pO_2 86 mm Hg) was present. However, the primary determinant of the systemic oxygen saturation is the amount of pulmonary arterial blood flow relative to the systemic blood flow (Qp/Qs). This accounted for 79% of the variability in systemic arterial saturation in Macartney's experience.

When the pulmonary artery can be entered, pressure measure-

ment allows an assessment of the degree of protection of the pulmonary vasculature. In many of these hearts the specialized conduction tissue runs around the anterior margin of the pulmonary valve annulus and complete heart block (usually temporary) may be provoked while manipulating the catheter into the pulmonary artery.

When severe stenosis or atresia of the AV valve draining the pulmonary venous atrium is suspected, catheterization should be performed in the neonatal period. The atrial septum is "softer" at this time and the likelihood of successful balloon atrial septostomy is greater. If the problem is not recognized until later in life, a blade[139] and balloon atrial septostomy may be attempted. The gradient between right and left atria must be abolished to decrease the symptoms of pulmonary venous hypertension.

Presently, inadequate pulmonary blood flow is managed by a surgical aorticopulmonary shunt. When pulmonary blood flow is limited by valvular pulmonary stenosis, it may be possible to use balloon techniques to relieve the stenosis partially and thus improve pulmonary blood flow without an operation. When pulmonary atresia is present and the ductus arteriosus has remained patent past the newborn period, but has shown evidence of constriction in its midportion, balloon ductal dilation may avoid or postpone the necessity for a shunt. We have successfully applied this technique to one patient with discontinuous pulmonary arteries arising from bilateral ductus. Nihill and coworkers have also successfully utilized balloon ductal dilation to avoid aorticopulmonary anastomosis. (Personal communication).

ANGIOGRAPHY

Angiography has played a major role in the development of our understanding of hearts with univentricular AV connection.[6,30,40,62,140–146] Quantitation of ventricular volume has been reported using angiographic techniques.[147–150] While echocardiography has emerged as a powerful tool for evaluating the anatomy of these hearts, angiography remains essential for the evaluation of details less well demonstrated echocardiographically. Angiography should be preceded by a complete echocardiographic examination. Often this is most efficiently obtained at the time of catheterization, while the child is sedated. The physician performing catheterization and angiography, thus guided, may use limited fluoroscopy time and contrast material to obtain essential information.

Anteroposterior and lateral cineangiography will provide delineation of many of the required details.[135,141] Axial angiography[151–156] allows clearer demonstration of AV valve anatomy, tiny ventricular chambers, outflow tracts and peripheral pulmonary arteries. The two most important views are the "four-chamber" view and the long axial oblique view.

The four-chamber view is obtained by sitting the patient up 35 to 45 degrees then raising the left shoulder by 35 degrees. The patient is then angled on the table so that the long axis of the heart becomes more parallel to the table. A similar relative position of tubes and patient can be obtained using a double C arm, however, the head tends to be more in the way than if the patient is sitting up and the neck hyperextended. In a biventricular heart, the four-chamber view profiles the inlet septum and separates the atria and ventricles. In hearts without an inlet septum the AV valves are usually well seen and their relation to the trabecular septum may be demonstrated. In addition, the left pulmonary artery is especially well defined by the anteroposterior tube in the four-chamber view. When abnormalities of the proximal left pulmonary artery are suspected this view should be used; it requires greater penetration of the liver than the other views. The liver collects contrast material and becomes more difficult to penetrate, requiring higher kilovoltage, with successive injections. The least Compton scatter and therefore the sharpest images will be obtained if this view is used for the first injection of contrast.

The long axial oblique projection applied to the normal heart gives information about the left ventricular outflow tract, and the more anterior portion of the ventricular septum. In the hearts with univentricular AV connection and normally related ventricles this view will profile ventricular septal defects well.

When echocardiography suggests dominant left ventricle with right-hand architecture, the initial injection may be made with the catheter in the left ventricle and the patient turned to provide the four-chamber view. If the AV valve anatomy is well demonstrated by echocardiography and there is no indication of left pulmonary artery abnormality, the standard anteroposterior view may be used first. This is especially true if there is severe pulmonary stenosis or atresia and knowledge of the great vessel anatomy is required to plan a shunting procedure. Finally, the long axial view will usually demonstrate the ventricular septal defect or ventricular septal defects and any right ventricular outflow obstruction (Fig. 74–11).

When there is a dominant left ventricle and the ventricles are inverted, the standard frontal and lateral views will provide excellent visualization of the ventricular septal defect, or defects, and the subarterial region of the right ventricle (Fig. 74–12). If there is a question concerning the AV valves the four-chamber view should be utilized and, if needed, should be done as the first injection. Though injection into the left ventricle will usually show structures well, the catheter can usually be manipulated through the ventricular septal defect and an injection into the right ventricle can be made. When there is a restrictive ventricular septal defect, a right ventricular injection may be necessary to force enough contrast material into the aortic arch to allow accurate diagnosis of coarctation or interruption.[157]

When a dominant right ventricle is present with a posterior nondominant left ventricle both four-chamber and long axial oblique views should be performed. When the left ventricle is leftward (normally related ventricles) it is usually best seen in the frames obtained by the lateral camera when the patient is positioned for the four-chamber view (Fig. 74–13). When the left ventricle is rightward (inverted ventricles), it is usually best seen by the anteroposterior camera when the patient is positioned for the long axial oblique view.

When echocardiography fails to demonstrate a second ventricular chamber, the initial view should be the four-chamber, followed if necessary by the standard frontal/lateral, and long axial oblique views (Fig. 74–14).

These views are recommended to demonstrate the ventricular and AV valve anatomy. In the fragile newborn we are often more interested in the anatomy crucial to planning a shunt procedure than anatomic details required for more definitive surgery. We may alter views to better demonstrate arch and pulmonary artery anatomy, and may defer some injections until later infancy or childhood.

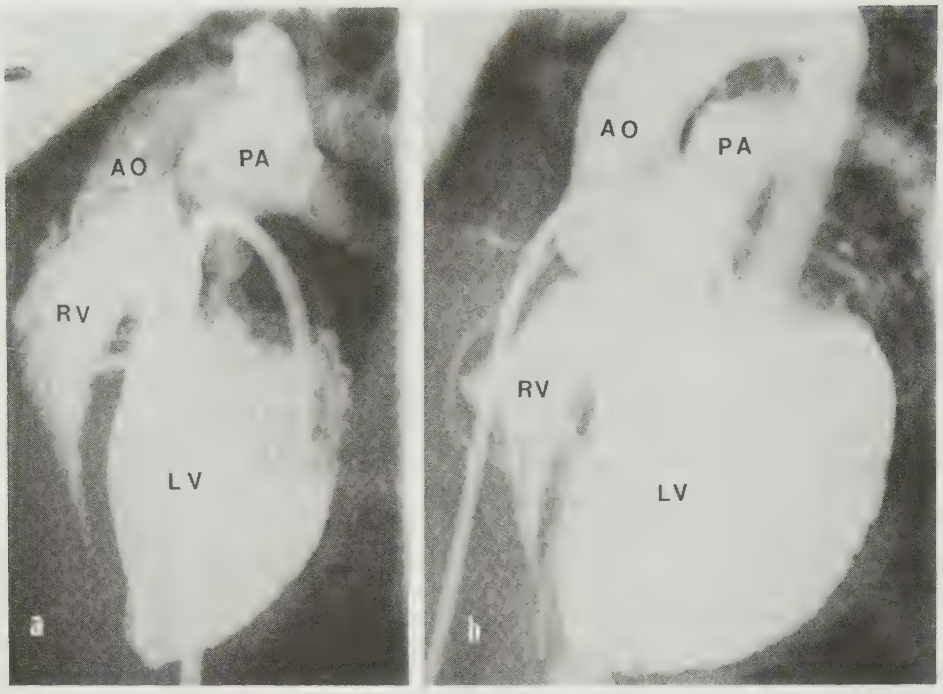

Fig. 74–11. Angiogram of a) double inlet to dominant left ventricle with right-hand architecture and ventriculoarterial discordance. The ventricular architecture is indistinguishable from a patient with b) classic tricuspid atresia. AO = aorta; PA = pulmonary artery; RV = right ventricle; LV = left ventricle.

NATURAL HISTORY

Case reports document survival into adulthood[158–161] and female patients have experienced successful pregnancies.[162,163] The most detailed information concerning the prognosis of patients with single ventricle not operated on is reported by Moodie et al.[101] These patients were in late childhood at the time of diagnosis and therefore had survived the high-risk neonatal period. Eighty-one percent of 83 patients had an outlet chamber (type A) and 19% did not (type C). Seventy-eight percent had no associated noncardiac lesions. Seven percent had asplenia. The most common associated cardiac lesion was pulmonary stenosis, present in 37% of patients with type A morphology. Most patients had exercise intolerance and cyanosis.

Fifty percent of patients with type A morphology were dead within 14 years after diagnosis, a death rate of 4.8% per year. For type C anatomy the prognosis was worse; 50% of patients died within four years of diagnosis. Of the patients in New York Heart Association (NYHA) class I or II at initial diagnosis, 34% with type A and 12% with type C were in class III or IV or had died at followup. Three patients had episodes of supraventricular tachycardia during followup and complete heart block developed in no patient. However, dysrhythmia or sudden unexplained death was the most common cause of death. Other causes included congestive heart failure, thrombotic occlusion of the pulmonary valve, brain abscess, pancreatitis, cerebral infarction, cerebral embolus and hemorrhage, and pulmonary embolus. In a companion study of patients give palliative treatment the causes of death were similar but also included endocarditis. Though palliation improved symptoms, survival was not greatly improved.

Atrioventricular valve insufficiency often appears and progresses over the first two or three decades in even patients with good palliation. This is presumed to be secondary to the left ventricular volume overload imposed by the need for a pulmonary blood flow of about twice normal. The tendency toward progression of subaortic stenosis in some patients is discussed more fully in the section of palliative surgery.

SURGERY

The dismal natural history for this group of patients has provided the motivation for the development of a number of palliative procedures and two more radical ''curative'' procedures.

Palliative Procedures

Palliative procedures include systemic-to-pulmonary-artery shunting, pulmonary artery banding, atrial septectomy, atrial switch procedures, superior-vena-cava-to-right-pulmonary-artery anastomosis, and a number of procedures to relieve subaortic obstruction. The latter include left-ventricle-to-descending-aorta conduits, resection of septal muscle to enlarge the interventricular communication, and anastomosis between the main pulmonary artery and the ascending aorta, usually combined with systemic-to-pulmonary-artery shunting. The goal in each is to provide relief of current symptoms and to allow survival to an age when a more ''curative'' procedure, if possible, may be performed with lower risk. Ideally, structural and functional changes induced by the palliative procedure should not adversely affect the risk of a subsequent ''curative'' procedure. It is therefore important to decide early in life which ''curative'' operations are possible for a given patient in order to establish the goals of early palliative surgery. Some patients will have an anatomy or physiology that precludes a more ''curative'' procedure. For these patients the palliative procedure will be the only surgical option available.

Problems that force palliation include cyanosis when pulmonary blood flow is restricted or streaming is unfavorable, congestive heart failure and the threat of pulmonary vascular obstructive disease when there is no restriction to pulmonary blood flow, pulmonary venous hypertension when the atrial septum is relatively intact and there is left AV valve stenosis or atresia, and subaortic

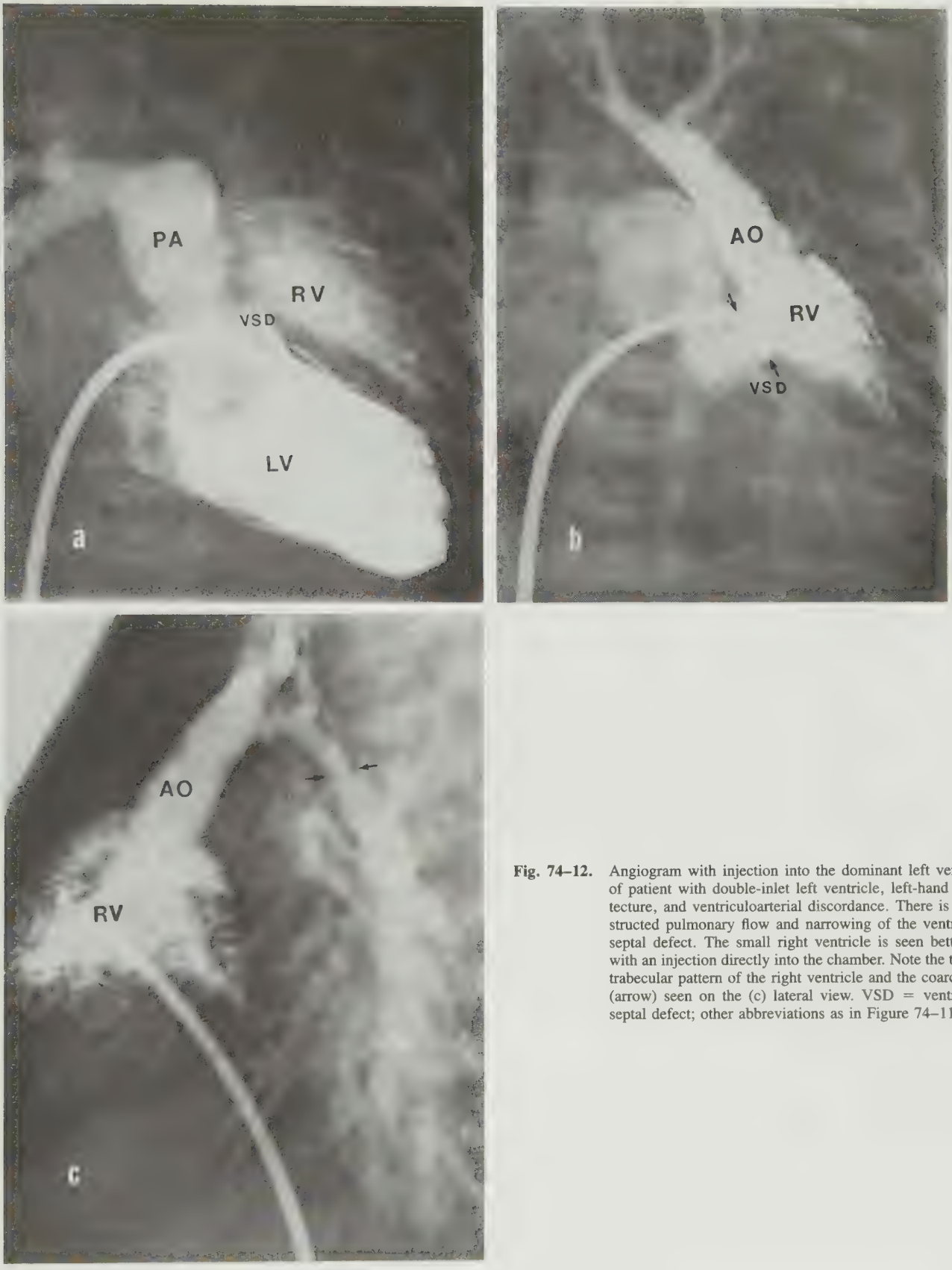

Fig. 74–12. Angiogram with injection into the dominant left ventricle of patient with double-inlet left ventricle, left-hand architecture, and ventriculoarterial discordance. There is unobstructed pulmonary flow and narrowing of the ventricular septal defect. The small right ventricle is seen better (b) with an injection directly into the chamber. Note the typical trabecular pattern of the right ventricle and the coarctation (arrow) seen on the (c) lateral view. VSD = ventricular septal defect; other abbreviations as in Figure 74–11.

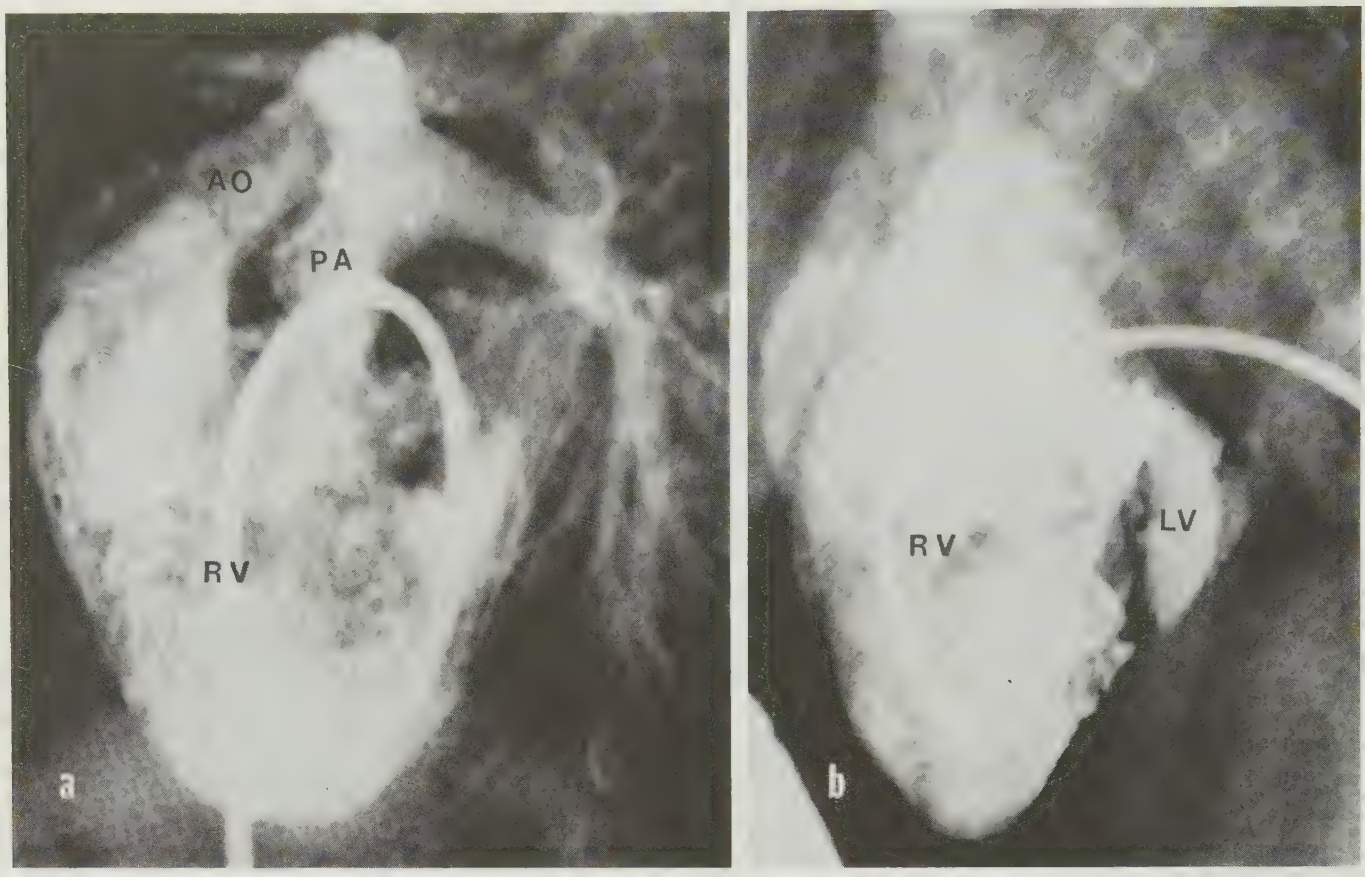

Fig. 74–13. This patient with dominant right ventricle and right-hand architecture was thought to have indeterminate ventricular morphology (a) until the view obtained by the lateral camera (b) in the four-chamber position revealed the small left ventricular chamber. Abbreviations as in Figure 74–11. (From Soto, B., Pacifico, A.D., and Di Sciascio, G.: Univentricular heart: An angiographic study. Am. J. Cardiol., *49*:787, 1982.)

obstruction usually secondary to a restrictive ventricular septal defect.

Operations to Increase Pulmonary Blood Flow

Kreutzer et al.[164] reported successful resection of pulmonary stenosis as palliation for three patients with reduced pulmonary blood flow. Each was alive six years postoperatively and two of the three were functionally normal. This method of increasing pulmonary blood flow involves an open procedure, and control of the amount of additional blood flow provided seems less precise than with a classic or modified Blalock-Taussig anastomosis. The possibility of partially relieving valvular stenosis by balloon catheterization techniques has the advantage of avoiding an operation, but the similar disadvantage of less control over the degree of shunting.

Systemic to Pulmonary Artery Shunts

Early reports[165–168] suggest mortality rates for shunt procedures performed on patients with single ventricle ranging from 8 to 50%. Villani et al.[165] reported a 20% mortality rate for shunting using Waterston shunts in young infants and classical Blalock-Taussig shunts for other children. If patients with major associated anomalies were excluded, the mortality was 8%, similar to the result in classic tricuspid atresia in the same period. Shunting was necessary twice as often as banding in this set of patients.

Crupi et al.[104] reported on a group of young patients (median age at surgery, 8.5 months) palliated with modified Blalock-Taussig or classic Blalock-Taussig shunts with an operative mortality of 8%. Actuarial survival of their group (including eight patients with successful pulmonary artery banding) was 80% at 10 years. Mazzucco et al.[169] reported 8% mortality with the same shunts, while neither of the two patients treated with a Potts or Waterston anastomosis survived.

Stefanelli et al.[41] and Kirklin and Barratt-Boyes[170] reported a 2% (confidence interval, 0.3 to 8%) operative mortality (1 death in 45 patients) for classic Blalock-Taussig or modified Blalock-Taussig shunting. Of the 45 survivors, 15 underwent at least one subsequent operation. During the same period, 18 nonclassic shunts were performed with 5 operative deaths (28% mortality, confidence interval, 16 to 43%). Actuarial five-year survival for a classic shunting procedure was 85%.

The long-term followup of these younger patients contrasts with the result when an older group is followed. Moodie et al.[110] reported on a large group of patients with a mean age at diagnosis of 10 years. Shunts included classic Blalock-Taussig, Potts, Waterston, and Glenn anastomoses. The estimated five-year survival rate (after diagnosis, not necessarily after procedure) in patients with an outlet chamber was 72%, and in patients without an outlet chamber 54%. Causes of death in 33 patients who had palliative surgery (shunting, banding, and/or septectomy) included conges-

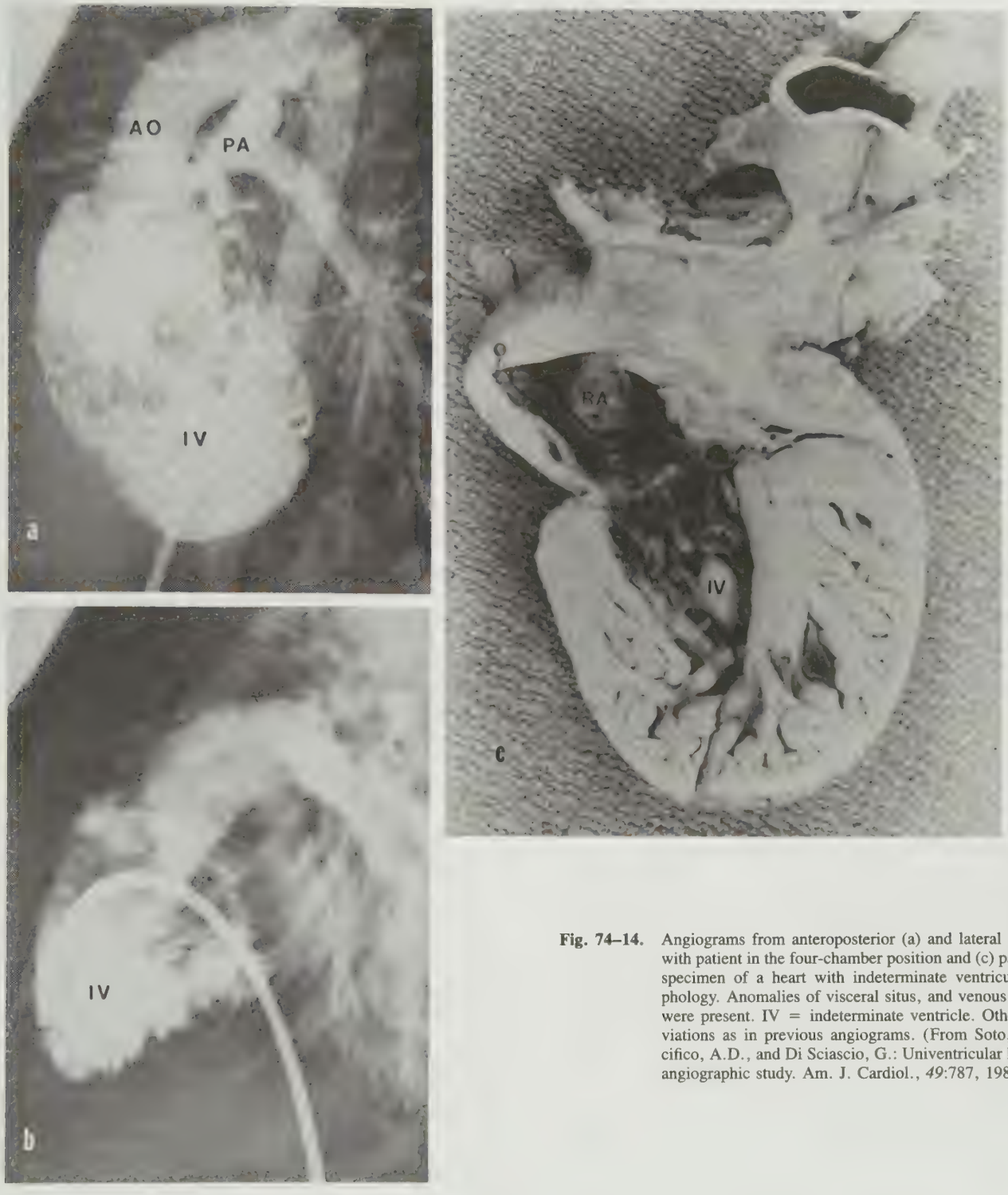

Fig. 74–14. Angiograms from anteroposterior (a) and lateral (b) tubes with patient in the four-chamber position and (c) pathologic specimen of a heart with indeterminate ventricular morphology. Anomalies of visceral situs, and venous drainage were present. IV = indeterminate ventricle. Other abbreviations as in previous angiograms. (From Soto, B., Pacifico, A.D., and Di Sciascio, G.: Univentricular heart: An angiographic study. Am. J. Cardiol., *49*:787, 1982.)

tive heart failure, dysrhythmia or sudden unexplained death, acute cerebral events, pneumonia, hypoxemia due to an occluded shunt, and endocarditis. Functional class I or II at diagnosis did not ensure longterm survival.

Taussig[171] reported followup of up to 27 years on 24 patients who underwent a Blalock-Taussig anastomosis for a single ventricle. The actuarial survival curve (Fig. 74–15) drawn from her data shows a 10-year survival for hospital survivors of 72% and a 20-year survival of 50%.

In summary, it is possible to perform classic and modified Blalock shunts on this group of patients with low operative risk. These shunts allow survival and growth of pulmonary arteries. Patients who are not candidates for modified Fontan or septation operations may remain palliated for many years, though second shunting procedures may be necessary. The importance of precise diagnosis prior to a shunting procedure is exemplified by two patients[104] with unrecognized total anomalous pulmonary venous return who died from pulmonary edema following shunting.

Pulmonary Artery Banding

Pulmonary artery banding was required much less frequently than shunting.[104,110,170,172] Dooley et al.[173] reported 11 survivors of 20 patients undergoing banding for a single ventricle. Lower early mortality rates have been reported by others.[104,165,169] Possible complications include inadequate reduction of pulmonary artery pressure with resulting pulmonary vascular obstructive disease,[169] distal migration of the band with resulting distortion of the proximal branch pulmonary arteries, and massive ventricular hypertrophy with resulting obstruction at the level of the ventricular septal defect.[174–177] Of the eight patients at risk in the report of Crupi et al.[104] only two developed subaortic obstruction. In the larger series of Freedom et al.,[176] 72% (31 of 43 patients) banded early in life (mean age at banding, 0.23 year) developed subaortic obstruction. In the subgroup of 32 patients with dominant left ventricle and ventriculoarterial discordance, 27 or 84% developed stenosis. The mean age at diagnosis of stenosis was 2.5 years.

Patients have been reported in whom an appropriate narrowing of the pulmonary artery failed to protect the pulmonary vasculature.[178,179] Late results in older patients reported by Moodie et al.[110] suggest a mortality rate five years after diagnosis (not necessarily after banding) of 32%. The causes of late mortality are listed in the section on shunts and are not broken down into banding versus shunting.

While the early operative risk is low, and adequate protection of the pulmonary vascular resistance may be obtained, the adverse effects on the ventricular septal defect and ventricular compliance have prompted the suggestion by Freedom[180] that pulmonary artery banding should not be performed as palliation when "curative" operation is planned and the anatomy is such that subaortic obstruction seems likely to develop.

Atrial Septectomy

Atrial septectomy is mentioned in several reports[110,165,169,181] with few cases and variable results. Stefanelli et al.[41] reported no hospital deaths in 14 patients who underwent a Blalock-Hanlon operation with or without associated closed procedure. Actuarial survival at 10 years was 75%. Five of the patients underwent at least one subsequent operation. Septectomy is usually undertaken to relieve left atrial hypertension when there is a restrictive atrial septal defect and stenosis or atresia of the valve draining the pulmonary venous atrium. In patients with unrecognized obstruction to the outlet of the pulmonary venous atrium shunt procedures may precipitate pulmonary edema. It is therefore important to recognize the need for septectomy at the time of initial diagnosis so that shunt and septectomy, if necessary, may be performed via the same thoracotomy. It has been suggested that septectomy might improve mixing in hearts with unfavorable streaming and intact atrial septum, but conclusive data are not available. It has also been suggested that in patients with unfavorable streaming a pal-

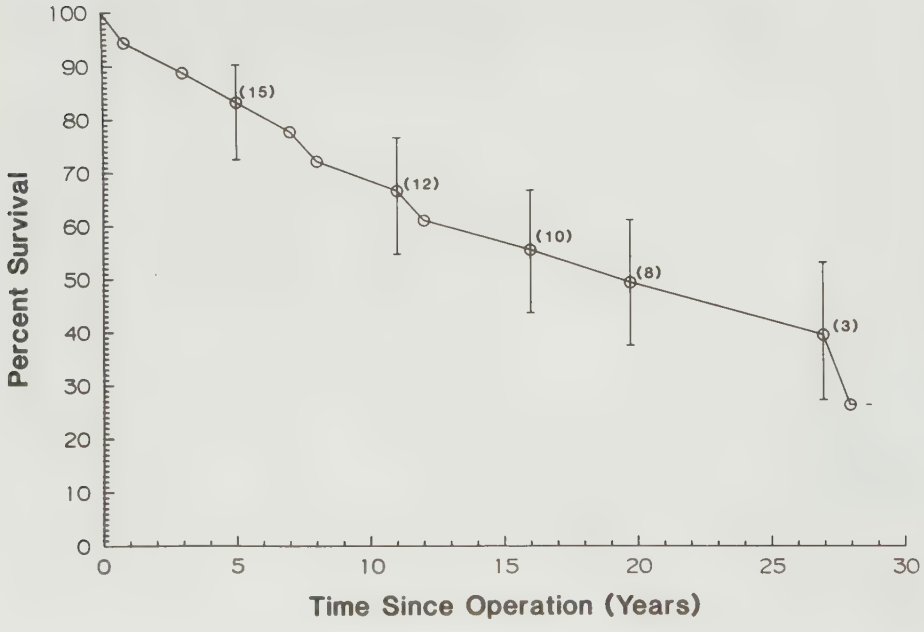

Fig. 74–15. Actuarial survival of hospital survivors of the Blalock-Taussig anastomosis for single ventricle. (From Kirklin, J.W., and Barratt-Boyes, B.G.: Univentricular atrioventricular connection (single ventricle). *In* Cardiac Surgery. New York, Wiley, 1986.) (Data from Taussig.[171])

liative Mustard or Senning operation might improve saturations.[182,183]

Glenn Shunt

While most patients are well served by classic or modified Blalock-Taussig anastomoses, there are patients who may be better served by a superior-vena-cava-to-right-pulmonary-artery anastomosis.[184–190] This procedure achieves an increase in effective pulmonary blood flow without placing an increased volume load on the ventricle.[191] This may be advantageous in the presence of significant AV valve insufficiency or mild ventricular dysfunction. When there is severe proximal right pulmonary artery stenosis that would be difficult to relieve at the time of a Fontan-type repair, a Glenn shunt may be used[189] in conjunction with a right-atrium-to-main-pulmonary-artery anastomosis to achieve a similar physiology. In fact, Fontan and Baudet[11] used a Glenn shunt in their first reported case and 17 of 100 patients reported on in 1983 had undergone previous Glenn shunting.[192] Anastomosis of the transected right pulmonary artery to the side of the superior caval vein, which is left in free communication with the right atrium, has been used.[193] This has the theoretical advantage of allowing the right lung (which receives two thirds of the total ventilation) to receive flow from both the upper and lower venous returns.

Hopkins et al.[194] reported use of a modification of the Glenn shunt in which the right pulmonary artery is not transected but left in continuity with the main pulmonary artery. Such a bidirectional shunt has the advantage of allowing the larger circulation of the right lung to receive blood from both the superior and inferior caval veins after the Fontan procedure. This bidirectional cavopulmonary shunt has been applied as a palliative procedure as well as at the time of Fontan operation. Twelve of 21 patients had classic tricuspid atresia and 9 had other forms of univentricular AV connection. All 12 patients undergoing palliative operation survived and were improved. Five subsequently underwent a Fontan operation, with no deaths. When the shunt was performed at the time of Fontan operation there were two early deaths and one patient died suddenly later.

Operations to Relieve Subaortic Stenosis

Subaortic stenosis is an ominous finding. Congenital presence of subaortic stenosis at the level of the ventricular septal defect has been described.[4] Early development of subaortic stenosis in the presence of congenital pulmonary stenosis has been documented as well.[177,195] As mentioned in the section on banding, the progression of stenosis is accelerated by banding.

When subaortic stenosis is present with or without previous banding,[196] a number of operations have been attempted to achieve palliation. Penkoske et al.[197] reported success in three patients treated by enlargement of the ventricular defect, in two patients with enlargement of the ventricular septal defect and placement of a left ventricular to descending aorta conduit, and in one patient by creation of an aortopulmonary window proximal to a previously placed pulmonary artery band. There were only 9 survivors of 31 patients who developed subaortic stenosis.

In a child with excessive pulmonary blood flow a modification[198] of the Norwood[199] procedure with transection of the main pulmonary artery, anastomosis of the proximal pulmonary artery to the aorta, and placement of a modified (5-mm Gore-Tex) Blalock-Taussig shunt to the distal pulmonary arteries has been performed. Alternatively, a graft has been placed from the proximal pulmonary artery to the descending aorta with banding of the proximal pulmonary artery.[200]

Lin et al.[201] reported on eight patients with subaortic stenosis treated by end-to-side anastomosis of the main pulmonary artery to the ascending aorta (Fig. 74–16). Preoperative gradients ranged from 10 to 80 mm Hg. Two operations were performed as palliative procedures within the first six months of life, while the other six were performed as a part of a definitive Fontan-type repair. The single death occurred following a palliative procedure performed at four months of age.

Barber et al.[202] described one patient who died following palliation with pulmonary-artery-to-aorta anastomosis and shunt. Four other patients, three of whom died, were treated similarly at the time of a Fontan-type repair.

Jonas et al.[203] described three patients successfully palliated by anastomosis of the pulmonary artery to the ascending aorta with placement of a shunt. Subsequently, Rothman et al.[195] described, more fully, experience at the Boston Children's Hospital with this problem. Of four children treated with a left-ventricle-to-descending-aorta conduit none survived. Four of the seven who had enlargement of a restrictive ventricular septal defect survived, but only one of four had adequate relief of stenosis and postoperative heart block was common. Six of 13 patients undergoing main pulmonary-artery-to-ascending-aorta connections survived and four have successfully undergone a modified Fontan procedure, while two await operation. The overall survival rate for all procedures was 42% and no patient with a gradient greater than 77 mm Hg survived any procedure. On the basis of their small but dismal experience with enlargement of the ventricular septal defect, they have chosen to palliate with a pulmonary-artery-to-aorta anastomosis. Whether patients palliated in this manner will fare better with subsequent septation or a modified Fontan operation remains to be seen.

"CURATIVE" PROCEDURES

Fontan–Kreutzer Operation

The original papers of Fontan[11] and Kreutzer[12] and their colleagues established the concept of using the single ventricle in tricuspid atresia to generate systemic blood flow while allowing pulmonary flow to occur directly from the right atrium to the pulmonary artery without an interposed ventricle. This concept was extended to the treatment of other forms of univentricular AV connection by Yacoub and Radley-Smith[13] and others.[204–211] As with the application of this concept to classic tricuspid atresia, the exact surgical details of the right-atrium-to-pulmonary-artery connection have undergone modifications.[212] While early operations were performed using valved conduits, most are presently done by direct anastomosis[213] and if necessary roofed with Dacron or Gore-Tex[170] or pericardium.[214] The major considerations presently recognized include creation of a generous anastomosis between the atrium and pulmonary artery, careful avoidance of compression of the anastomosis by sternum or thymus, and avoidance of the sinus node artery on the roof of the atrium

In cases with two competent and nonstenotic AV valves the right valve may be closed by direct suture of valve leaflets[215] or a patch sewn to valve tissue or to atrial myocardium several mil-

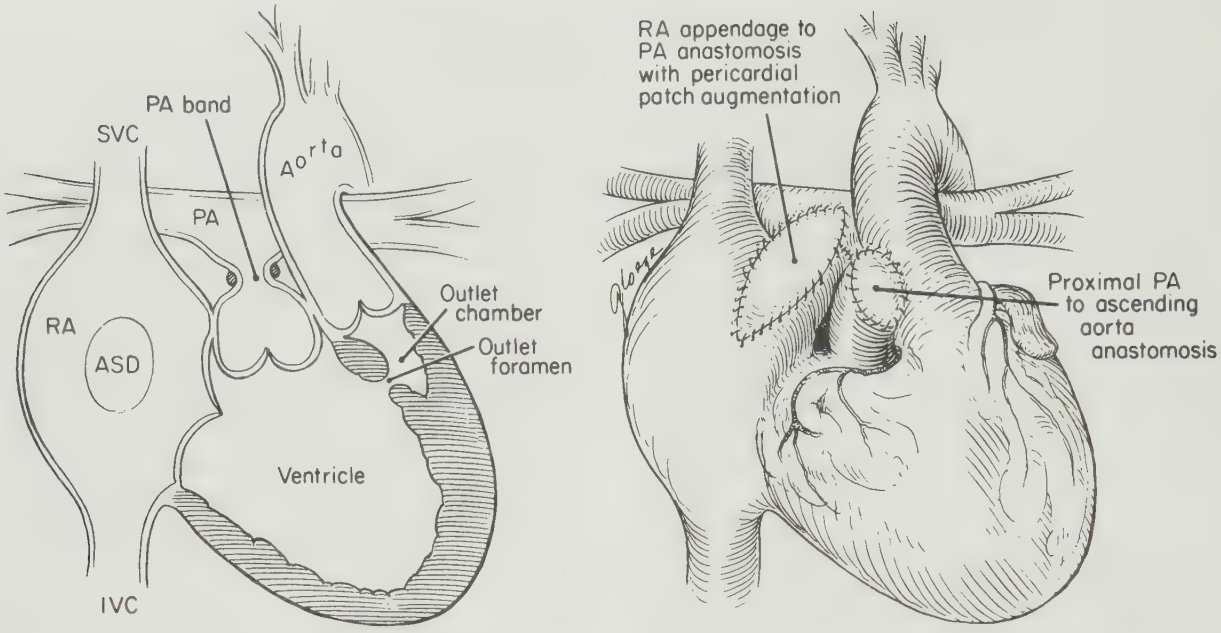

Fig. 74–16. Diagram of Fontan-type operation with anastomosis of main pulmonary artery to ascending aorta for a patient with subaortic stenosis and single ventricle. PA = pulmonary artery; SVC = superior vena cava; RA = right atrium; ASD = atrial septal defect; IVC = inferior vena cava. (From Lin, A.E., et al.: Subaortic obstruction in complex congenital heart disease: Management by proximal pulmonary artery to ascending aorta end to side anastomosis. J. Am. Coll. Cardiol., *7*:617–624, 1986.)

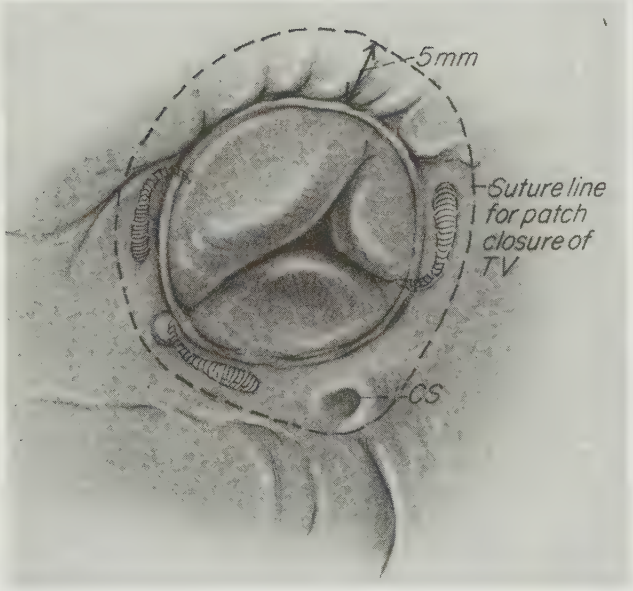

Fig. 74–17. Technique for closing the right atrioventricular valve with Fontan-type operation for single ventricle. TV = tricuspid valve; CS = coronary sinus. (From Kirklin, J.W., and Barratt-Boyes, B.G.: Univentricular atrioventricular connection (single ventricle). *In* Cardiac Surgery. New York, Wiley, 1986.)

limeters outside the annulus (Fig. 74–17). The latter technique is presently preferred, since dehiscence is less likely and AV block due to damage of the AV node is usually avoided.[170,204,214,216] Closure of the right AV valve is mandatory if the valve is insufficient. If both valves are competent, then a baffle may be placed in the atrium leaving both valves receiving pulmonary venous blood and allowing egress into the ventricle (Fig. 74–18). This type of connection must be used if the left AV valve is absent or stenotic. If the atrial baffle is too redundant it will obstruct one pathway or the other.[216] More recently, a technique has been devised using part of a woven Dacron conduit as one wall and the lateral atrial wall as the other to create a tubular conduit to direct the inferior caval flow to the roof of the atrium.

The problem of subaortic stenosis, usually at the level of the ventricular septal defect, has been mentioned in the section on palliative surgery. Main pulmonary-artery-to-aorta anastomosis[217] has been used at the time of modified Fontan operation.[13,181,197,201,202,218,219] Enlargement of the ventricular septal defect also has been performed concomitantly with a modified Fontan procedure. Clearly, the presence of a significant gradient is associated with a hypertrophied, noncompliant ventricle and high operative mortality.[220] The operative mortality in the group of cases from the literature summarized by Barber et al.[202] was 60% (9 of 15 patients). In their own experience, the surgical mortality rate was 56% (10 of 18 patients), of which 13 had a modified Fontan procedure, 3 a septation, and 1 an aorta-to-pulmonary-artery anastomosis combined with enlargement of the ventricular septal defect. Neither patient with aorta-to-pulmonary-artery anastomosis survived. Those who did survive were usually symptomatic.

The series reported by Lin et al.,[201] in which five of six patients undergoing pulmonary-artery-to-aorta anastomosis with modified Fontan operation survived, is a source of some optimism.

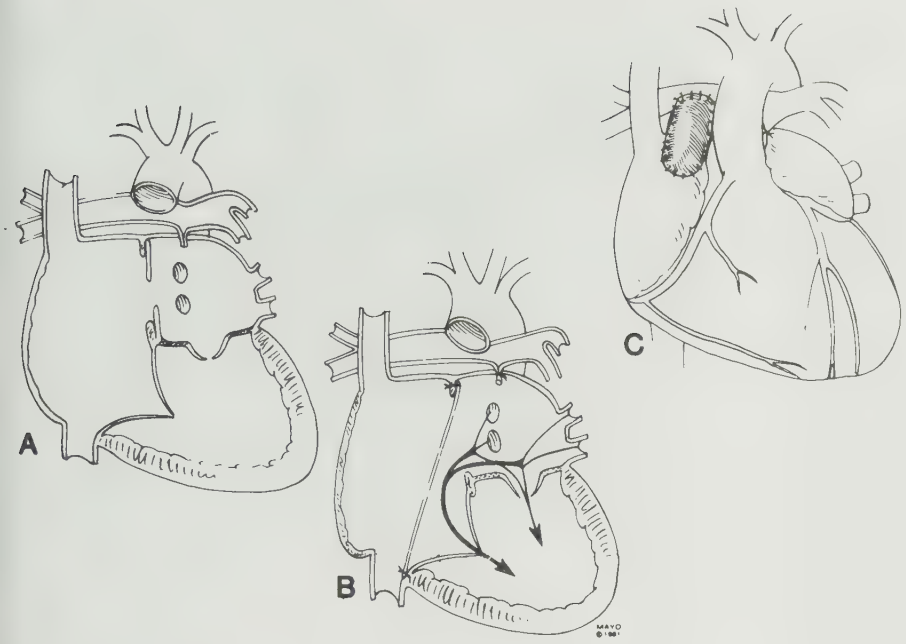

Fig. 74–18. Position of the baffle in hearts with a stenotic left atrioventricular valve. Note the potential for bulging of the baffle and partial obstruction of the right atrioventricular valve. (From Danielson, G.K.: Surgical management of double inlet ventricle. *In* Double Inlet Ventricle. Edited by R.H. Anderson, G. Crupi, and L. Parenzan. Tunbridge Wells, Kent, Castle House Publications, 1987.)

Danielson[214] reported an early mortality of 10% for a modified Fontan procedure for double-inlet left ventricle when all 10 ideal criteria[221] were met. Mortality was greater than 50% when three or more criteria were not met. He comments that only one fifth of his patients fulfilled all criteria. The absence of sinus rhythm was not found to be a contraindication to operation[222] and permanent pacing techniques have been applied postoperatively.[110,223,224] The two most important criteria require normal pulmonary arteriolar resistance, and adequate size and distribution of the pulmonary arteries. In the Mayo Clinic experience,[214] the operative mortality has improved from 30% for the first 92 patients with double-inlet left ventricle to 9% for the 57 patients operated on between April 1982 and April 1984. This improvement may be due to better selection of patients or better operative and postoperative techniques.

The overall 29% mortality in Kirklin and Barratt-Boyes' experience[170] using a modified Fontan procedure for a single ventricle is similar to that at the Mayo Clinic and other published experiences.[204,206,208] More recent experience from January to November 1983 with a mortality rate of 7% (confidence interval, 1 to 22%) would support the idea that results from this procedure are improving.

For the Fontan procedure in general, death after hospital discharge is uncommon and actuarial late survival of hospital survivors is 92%. If hospital deaths are included in the actuarial survival, survival at 5 years has been 71% (95% confidence, ±6%), and with current techniques is anticipated[170] to approach 90%.

Late problems include ventricular dysfunction,[225] AV valve insufficiency, atrial arrhythmia, and protein-losing enteropathy.[214] Catheterization has documented an improvement in mean left ventricular end diastolic pressure, presumably as a result of relief of volume overload. More than 90% of survivors[170,208,214] are in NYHA class I or II. Exercise testing in survivors was normal in Kreutzer's experience[164] and mildly subnormal in the Mayo Clinic experience.[214,226,227]

While no large series of patients with significant systemic and pulmonary venous anomalies treated with Fontan-type operation has been reported, case reports of success[228–230] have been reported. Valve replacement was necessary in some cases with insufficient common AV valve. Successful pregnancy was reported[229] in one such patient six years postoperatively.

Septation

A case of single ventricle encountered unexpectedly (preoperative diagnosis was corrected transposition and ventricular septal defect) at the Mayo Clinic in 1956 was repaired by dividing the ventricle.[231] The patient died six months after surgery, presumably due to a Stokes–Adams attack. In the early 1970s several reports of success[78,232–234] prompted renewed interest in this approach. The right atrial approach to septation was suggested and applied.[235]

Overall operative mortality was high during the early experience: 47% (21 of 45 patients) at the Mayo Clinic[111] and 44% (7 of 16 patients) in the University of Alabama Birmingham[236] experience. Operative technique improved with transatrial approach, or "fish-mouthed" ventriculotomy to avoid coronary artery injury.[42] Small ventricular size and presence of outlet obstruction emerged as risk factors in the University of Alabama Birmingham experience. The Mayo Clinic experience identified preoperative congestive heart failure, and previous palliative surgery as significant risk factors. Polycythemia and preoperative or postoperative complete heart block were not found to be risk factors. Operative mortality was increased if there was need for valve replacement or placement of a valved external conduit. Complete heart block was present preoperatively in 3 of 32 patients, and postoperative heart block occurred in 25 of 28 patients at risk in the University of Alabama Birmingham experience.[170] Though the differences in survival for different morphologic subgroups have been too small to prove statistical significance,[11,170] no survivors were present among the anatomic subgroups with no outlet chamber in the Mayo Clinic experience. Reoperation was required for patch dehiscence and valve dysfunction.[237] There were several late

postoperative sudden deaths and only 7 of 16 late survivors were asymptomatic. Multivariate analysis of the Mayo Clinic experience identified a subgroup of 11 patients who had good results from operation—82% survival. These patients had a subaortic chamber to the left, no previous congestive heart failure, no previous palliative operation, no profound polycythemia, and ranged from 5 to 15 years of age at the time of operation. On the basis of these findings, the Mayo Clinic established the practice of performing modified Fontan operation when possible and reserving septation for patients with modestly elevated pulmonary vascular resistance.

Stefanelli et al.[41] described a similar outcome for an ideal set of patients with a large left ventricle, normal situs, and left-sided subaortic chamber with no associated defects. Among these, there were no hospital deaths and 77% (confidence interval, 59 to 90%) were alive after a median followup of 2 years. There were two late sudden deaths. Two patients in this group required reoperation for patch dehiscence. All of the surviving patients were in NYHA class I or II. Detailed hemodynamic studies[238] support the possibility of good functional status after septation, as do animal studies[239–241] in which the septum was replaced without detriment to ventricular function.

In 1984, Ebert[103] reported a two-stage approach, which he applied to hearts with "common ventricle." In infancy, a patch is placed at the apex and a second patch between the AV valves. Widely spaced sutures are used. A pulmonary artery band is placed. A second stage is undertaken 6 to 18 months later, at which time the "ventricular septal defect" is closed and the band removed. All four patients survived with sinus rhythm. It is uncertain if the morphology in these patients would have led to heart block if a single-stage repair had been undertaken. Forthcoming further experiences will certainly be of great interest.

Current operative technique has been outlined by Pacifico et al.[242,243] (Fig. 74–19). The location of the suture line superiorly is dictated by the location of the aterial valves and inferiorly by the location of the papillary muscles and chordal apparatus, thus the surgeon has little control over the amount of ventricle allocated to the right and left sides. The size of the patch is critical, since too large a patch will bulge and possibly obstruct the right outflow. Too small a patch will be more likely to dehisce. If the great vessels are not appropriately placed for a straight patch, a spiral patch may be used. Alternatively, a straight patch has been used with concomitant atrial switch with good result.[242] Intraoperative mapping of the conduction system has been used, but this is not possible when repair is performed through the atrium.

Subpulmonic stenosis may be resected in many patients but an external valve conduit may be required to connect the new "right" ventricle to the pulmonary arteries. Operative mortality is higher (67% with 44 to 85% confidence interval) when a conduit is required.[242]

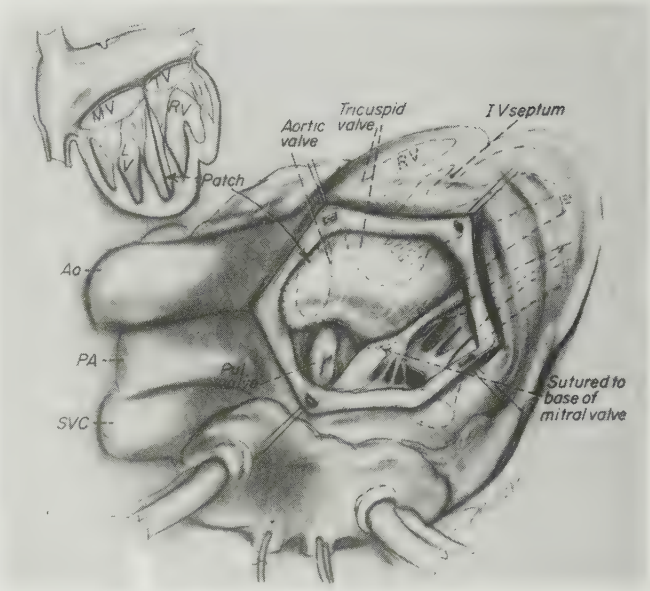

Fig. 74–19. Location of the patch in the septation operation for double-inlet left ventricle with left-hand architecture and ventriculoarterial discordance. MV = mitral valve; TV = tricuspid valve; RV = right ventricle; LV = left ventricle; IV = interventricular; Ao = aorta; PA = pulmonary artery; Pul = pulmonary; SVC = superior vena cava. (From Pacifico, A.D., Soto, B., and Bargeron, L.M., Jr.: Surgical treatment of straddling tricuspid valves. Circulation, *60*:655, 1979.)

CURRENT PRACTICE

Controversy still exists concerning the best approach to the patient with two good AV valves. For a patient with low pulmonary vascular resistance, a mildly dilated ventricle, no AV valve insufficiency, no subaortic stenosis, and resectable subpulmonary stenosis, the operative risks of septation and the Fontan-type operation are similar. The need for a valved external pulmonary conduit or AV valve replacement sigificantly increases the risk of septation. On the basis of morphology alone,[244,245] the Fontan procedure is applicable in many more patients than the septation operation. Improved operative risk following the Fontan–Kreutzer type operation, and the good late results make this our present operation of choice for patients in whom either operation could be applied. Palliative procedures are chosen to allow survival, alleviate symptoms, and preserve the anatomy and physiology for later Fontan repair.

In neonates presenting with cyanosis in spite of adequate ventilation and high inspired oxygen concentation, and in whom the diagnosis of cyanotic congenital heart disease is highly suspected, prostaglandin E_1 infusion is begun before transport to the cardiovascular center. Initial evaluation is by two-dimensional and Doppler echocardiography.

If echocardiography demonstrates pulmonary atresia or severe stenosis, catheterization and angiography are undertaken to define the distal pulmonary artery anatomy, arch anatomy, and pulmonary venous connection. If associated left AV valve stenosis or atresia is present and the atrial septum is relatively intact, a balloon atrial septostomy is attempted. A modified Blalock-Taussig shunt is placed within 48 hours of diagnosis, usually on the same side as the aortic arch. If pulmonary venous return is obstructed at the level of the atrial septum (with left AV valve stenosis/atresia) and this cannot be relieved by balloon septostomy, then surgical resection of the atrial septum is performed. If obstructed total anomalous venous return is present, this is repaired. As the patient grows, cyanosis usually progresses. A second shunt, either modified or classic Blalock-Taussig, may be required. Repeat cathe-

terization is required to document the status of the branch pulmonary arteries following shunting procedures.

If ventricular function, AV valve competency, and pulmonary vascular structures are acceptable, elective Fontan operation is planned between two and five years of age. Secure information concerning elective Fontan-type repair for younger children is not presently available but may in the future reduce the age for elective operation.

If moderate pulmonary stenosis is seen by echocardiography and adequate oxygen saturation is present on room air, catheterization may be safely postponed. Continuous-wave Doppler examination may be used to document pulmonary artery pressure when the ventricular pressure is known and the gradient is estimated. Later in infancy, elective catheterization and angiography are undertaken to confirm echocardiographic diagnoses and to evaluate details of systemic venous, pulmonary venous, and pulmonary arterial anatomy less securely evaluated by echocardiography. If the echocardiographic and Doppler data do not securely establish the presence of low pressure in the pulmonary artery, then catheterization should be planned earlier, within the first three months of life. If pulmonary artery flow and pressure require reduction, banding is considered.

If early evaluation reveals no pulmonary stenosis, the ventricular anatomy assumes a great importance. Catheterization is usually performed in the first three months of life. If there is no suggestion of subaortic stenosis and the anatomy seems unlikely to lead to stenosis, then pulmonary artery banding may be undertaken. Careful followup for any evidence of subaortic stenosis is necessary. Banding will more likely be a reasonable option when the dominant ventricle is of right or indeterminate morphology.

When there is a dominant left ventricle and the aorta arises from the nondominant chamber and the ventricular septal defect is huge, banding may be considered. If the ventricular septal defect is small or of moderate size, banding seems likely to result in progressive subaortic stenosis and other options must be considered. At present, inadequate data exist to make secure recommendations. However, we would presently perform a pulmonary-artery-to-aorta anastomosis and provide pulmonary blood flow by a modified Blalock-Taussig shunt. Alternatively, if two good AV valves are present, one might proceed with a two-stage approach to septation as reported by Ebert.[103] In an older patient, enlargement of a restrictive ventricular septal defect may be possible.

Patients with severe coarctation also require repair in the neonatal period. When coarctation is associated with severe subaortic stenosis, a modification of the Norwood operation for hypoplastic left heart may be applied.

We presently reserve septation as an option for older patients with optimal internal anatomy and moderate elevation of pulmonary artery resistance for whom Fontan repair is not advisable. If there is resectable pulmonary stenosis and if the ventricle does not appear enlarged on chest roentgenography, a Blalock-Taussig shunt may be placed to induce ventricular enlargement.[148] Septation with resection of subpulmonary stenosis is then undertaken six months to one year later. If AV valve replacement or a valved external pulmonary conduit is required, septation may be attempted (recognizing higher operative and late risk).

Many patients are not acceptable candidates for either septation or Fontan-type repairs. In older patients with cyanosis and pulmonary artery abnormalities that prevent a Fontan operation, the Glenn shunt must not be forgotten. When distal pulmonary arteries are preserved and venous anatomy is not too complex, but ventricular function is failing, cardiac transplantation may be considered.

Finally, these hearts might possibly be noticed on prenatal obstetrical ultrasound scanning. At present, a quite accurate prenatal anatomic diagnosis could be made with subsequent high-resolution scanning and Doppler echocardiography. Options are now limited to counseling and planning peripartum and postnatal management. However, as the technology for prenatal intervention improves, the opportunity to alter, prenatally, the severe associated left outflow obstruction may benefit some of these patients.

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CHAPTER 75

Cardiac Malposition and Heterotaxy

Howard P Gutgesell

CARDIAC MALPOSITION

Terminology

Cardiac malposition has fascinated clinicians, pathologists, and embryologists for centuries. The abnormal location of the heart within the body is frequently associated with complex intracardiac anomalies and the absence, duplication, or abnormal location of the other viscera. Apart from their obvious challenge to the clinician, these conditions represent the ultimate test for any system of nomenclature and classification of congenital heart disease. Unfortunately, comprehending the literature that describes the cardiac malpositions is often more difficult than understanding the lesions. The following review of terminology gives the reader a basis on which to interpret the large, and sometimes confusing, body of literature pertaining to cardiac malposition and heterotaxy.

cardiac malposition: Location of the heart anywhere other than its usual position in the left hemithorax, or location of the heart in the left hemithorax when other organs are in an abnormal position such as situs inversus.

concordant, discordant: These terms commonly are applied to relations between atria and ventricles and between ventricles and great arteries. A right atrium connected to a right ventricle is concordant (normal), whereas a right atrium connected to a left ventricle is discordant. Thus, in situs solitus of the viscera and atria, the terms *L-loop ventricles* and *atrioventricular discordance* are essentially synonymous since they each describe a right atrium connected to a left ventricle and a left atrium connected to a right ventricle.

dextrocardia, levocardia, and mesocardia: These are general terms indicating the cardiac position only. They do not, in themselves, describe intracardiac anatomy. Dextrocardia denotes a heart in the right chest, levocardia a heart in the left chest, and mesocardia a midline heart.

d-loop; l-loop: These terms refer to the folding of the embryonic cardiac tube at about 23 days gestation. The loop normally bends toward the right (dextrally, d-loop). As a result, that portion of the primitive heart tube destined to become the right ventricle normally lies to the right of the anatomic left ventricle. If the cardiac tube bends to the left (l-loop), the future anatomic right ventricle lies to the left of the future anatomic left ventricle. A d-loop is normal in situs solitus and an l-loop is expected or "normal" in situs inversus.

heterotaxy: An abnormal arrangement of body organs that is different from the orderly arrangements of situs solitus or situs inversus. Typically, there is duplication or absence of normally unilateral structures (especially the spleen). Many authors have used the terms *situs ambiguous (ambiguus* if Latin is preferred) or *indeterminate situs* to describe this condition.[1–7]

inversion: Unfortunately, the term *inversion* has been used in two different ways to describe cardiac abnormalities. Several authors[18–21] have used this term to mean inverted relative to the usual relationship *within the body.* That is, a relationship in which the anatomic right ventricle lies to the left of the anatomic left ventricle is said to represent ventricular inversion. Others,[12] including Mullins in Chapter 73 of this text, use the term *ventricular inversion* to describe an abnormal relation of ventricles *to the atria,* irrespective of their position within the body (i.e., a discordant atrioventricular connection). Thus, the term *inversion* is ambig-

uous, and it should probably be replaced by less confusing terminology.

isomerism: The presence of paired, mirror-image sets of normally unilateral structures such as the lungs and atria. Left isomerism refers to the presence of two anatomic left lungs and two anatomic left atria, whereas right isomerism implies bilateral right lungs and atria. These terms are preferred by some[8] to polysplenia syndrome (for left isomerism) and asplenia syndrome (for right isomerism). (See discussion below.)

situs inversus: An arrangement of organs that is the mirror-image of normal (i.e., heart, stomach, and spleen on right; liver on left).

situs solitus: The usual or normal location of organs and vessels within the body (heart on left, liver on right, spleen on left, etc.).

transposition, transposition of the great arteries: Despite the frequency of this condition among patients with congenital heart disease, it has been difficult to formulate a universally accepted definition. Most definitions have been based upon one of the following concepts:

1. The interrelationships of the great arteries in space. Transposition has been defined as an anterior aorta and a posterior pulmonary artery.[9–12] Note that some investigators[13] use this definition literally, irrespective the ventricular origin of the great arteries. The term *malposition* has been used[14–16] to indicate an abnormal spatial relation between the aorta and pulmonary artery, without specifying their ventricular origins (thus, d or l malposition of the aorta).
2. The connections of the great arteries to the ventricles. Transposition has been defined as origin of the aorta from the right ventricle and origin of the pulmonary artery from the left ventricle (*trans* = across, *ponere* = to place). Thus, transposition is considered present when the great arteries are placed across the ventricular septum compared to normal.[5,6,14,16–18]
3. Physiology. Return of the systemic venous blood to the aorta and pulmonary venous blood to the pulmonary artery may be called transposition. Since this definition is not applicable to postmortem specimens, it is not used widely despite its obvious clinical importance. The term *complete transposition* also has been used to describe this form of physiology as distinguished from *corrected* transposition. The latter term has been applied to conditions such as situs solitus of the atria, atrioventricular discordance, and ventriculo-arterial discordance, in which systemic and pulmonary venous blood is directed appropriately to the pulmonary artery and aorta, respectively.

The nomenclature used to describe congenital abnormalities has evolved over several centuries. Until the 1960s and 70s, it was customary to describe cardiac malformations as discrete entities (e.g., "mitral atresia," "corrected transposition"). However, there are an almost infinite number of congenital malformations of the heart. Therefore, recent students of cardiac pathology have developed systematic classification systems designed to describe any cardiac malformation, however complex.[4–7,23] The segmental approach to the description of cardiac defects introduced by Van Praagh[3,21,24,25] forms the basis of virtually all current nomenclature schemes. Using this method, hearts are described according to three major segments and the connections between these segments:

1. visceroatrial situs (i.e., the location of the viscera and atria).
2. the ventricular anatomy, including the relationship of the ventricles to each other and their connections to the atria.
3. the conotruncus, which includes the locations of the infundibulum and great arteries.

The possible descriptions for each segment are outlined in Table 75–1. Note that although the situs may be "ambiguous" to the clinician, it is generally either left or right isomerism to the pathologist. Additionally, it is apparent that in visceroatrial situs solitus or inversus the terms *atrioventricular concordance* or *discordance* suffice to describe the atrioventricular relationship. In left or right atrial isomerism, however, these terms are not applicable and a designation of the type of ventricular looping is required. Finally, note that the terms are totally independent of the terms *dextrocardia, mesocardia,* and *levocardia,* which simply designate the location of the heart within the body.

Implicit in the descriptions of hearts by this method is the understanding that the bronchial tree, lungs, atria, and ventricles are named on the basis of their *anatomic* features rather than their *location* within the body. This concept, assumed by pediatric cardiologists and pathologists, is often confusing to others. It appears to have originated with Lev's study of cardiac malposition in 1954,[26] and it is hard to improve upon his explanation:

> A chamber cannot be designated according to the vessel of entry or exit, nor according to the valve of entry or exit, since these are variables in congenital heart disease. Likewise, a chamber cannot be designated according to its function since this is also a variable. The only sound method available is to designate a chamber according to its morphology.

Fortunately, all of the modern classification systems agree on this point. The pertinent anatomic features can be summarized as follows:

1. A right lung typically has three lobes and contains an eparterial bronchus that passes over the right pulmonary artery. A left lung has two lobes and does not contain an eparterial bronchus. The undivided left main stem bronchus is typically at least twice as long as the undivided right mainstem bronchus.[27,28] The situs of the lungs can be determined ra-

Table 75–1. Possible Variations in the Three Major Cardiac Segments

Visceroatrial situs
Solitus
Inversus
Heterotaxy (ambiguous, indeterminate)
Right isomerism
Left isomerism
Atrioventricular relationship
Concordant (d-loop ventricles in atrial situs solitus, l-loop ventricles in situs inversus)
Discordant (l-loop ventricles in atrial situs solitus, d-loop ventricles in situs inversus)
Ambiguous
Left or right atrial isomerism
Primitive ventricle
Great arteries
Normally related
Transposed
Double outlet
Single arterial trunk

diographically by using overpenetrated chest roentgenograms or tomography to delineate bronchial anatomy: the left lungs having long unbranched mainstem bronchi.[1,27–29]

2. An anatomic right atrium contains a crista terminalis and the limbus of the fossa ovalis. The appendage is broadbased and contains pectinate muscles. A left atrium lacks a crista terminalis and generally has a narrow-based appendage, which lacks pectinate muscles. The details of atrial anatomy are somewhat difficult to depict by current imaging techniques. Therefore, atrial anatomy usually is inferred from bronchial anatomy because of the very high degree of concordance between the "sidedness" of the bronchi and that of the atria.
3. The right ventricle is characterized by coarse trabeculations, a muscular conus separating the semilunar valve from the atrioventricular valve, and a tricuspid valve with some chordae that attach to the ventricular septum. A left ventricle has fine trabeculations, no conus (i.e., there is normally aortic–mitral fibrous continuity), and a mitral valve that attaches to two papillary muscles (and not to the septum).

Fortunately, the aorta and pulmonary artery have unique names that are unrelated to their usual location within the body.

Dextrocardia

Historical Aspects

The first reported cases of dextrocardia in humans appear to be those of Fabricius in 1606 and Servius in 1643.[30] The first classification system of dextrocardia was developed in 1749 by Senac,[31] who divided right-sided hearts into congenital and acquired forms. Numerous case reports appeared in the nineteenth century, and by the early twentieth century the literature contained several detailed classification systems.[32–35] Lichtman's review in 1931[36] contains no fewer than 370 references.

The clinical recognition and evaluation of dextrocardia was facilitated greatly by the development of roentgenography and electrocardiography. By 1915, both of these techniques had been applied to patients with dextrocardia.[37] Diagnostic accuracy has improved progressively as angiocardiography,[38–46] echocardiography,[47–51] and computed tomography[52,53] have been used to study patients with dextrocardia.

Incidence, Genetics, and Etiology

The incidence of situs inversus has been estimated as between 1/2500 and 1/20,000 living persons,[54–57] with 1/7000–1/8000 the most common estimate from mass radiographic surveys of adults.[56,57] Dextrocardia with situs solitus (isolated dextrocardia) is thought to be less common, with incidence estimates of 1/7500,[54] 1/17,500,[58] and 1/29,000.[57] In contrast, among patients referred to pediatric cardiology clinics, those with isolated dextrocardia are seen more commonly than those with situs inversus. This is, no doubt, related to the much higher incidence of intracardiac abnormalities in the former group. Campbell and Deuchar[59] identified 29 patients with dextrocardia in a group of 1130 patients with congenital heart disease (2%). Ten of these had situs inversus, 16 had situs solitus, and 3 had situs ambiguous.

In the autopsy series tabulated by Van Praagh,[21] there were 136 cases of dextrocardia: 66 had situs solitus, 24 situs inversus, and 46 situs ambiguous. Among 43 autopsied cases of dextrocardia, Stanger et al. found situs solitus in 12, situs inversus in 11, and asplenia/polysplenia in 20. Thus, although isolated dextrocardia is rare in mass radiographic surveys, it is the most common form of dextrocardia in young patients dying from congenital heart disease.

The genetic basis of dextrocardia in humans is unknown. Cockayne[60] believed that situs inversus was an autosomal recessive trait, citing the familial incidence and distribution within families, occurrence in 5 of 6 pairs of monozygotic twins, and a high incidence of first cousin marriages. Others have questioned this hypothesis,[57,61] largely because of the low incidence in siblings of propositi (1/51 to 1/91). More than one genetic mechanism may be operant: Workany[62] notes that although situs inversus behaves like a recessive trait in many families, in others it appears to be autosomal-dominant. Conversely, the relatively low incidence of concordance in monozygotic twins in his series (6 of 12 reported pairs) suggested that nongenetic factors play a role in the expression of situs inversus.

Little is known about the etiology of genetics of dextrocardia with situs solitus. Lowe and McKeown[57] found neither familial recurrences nor parental consanguity in their cases. Presumably, the recurrence risk is the same as that for congenital heart disease in general, 2 to 4%.[63]

The genetics of situs inversus in mice has been reviewed by Layton.[64–66] Situs inversus is inherited as an autosomal recessive trait. The normal allele at the *iv* locus (+/*iv*) causes situs solitus (normal laterality). Fifty % of mice homozygous for the gene *iv* (i.e., *iv*/*iv*) have situs inversus, and 28% have heterotaxia of major veins and abdominal organs. Major cardiac abnormalities occur in a high percentage of newborn mice with the iv/iv genotype. Layton hypothesized that the normal allele (+/*iv*) specifies situs solitus. In the homozygous state, this control is absent and situs is determined in a totally random manner. Thus, with the iv/iv genotype, situs solitus and situs inversus occur with equal frequency.

Embryology

The primitive cardiac loop normally bends toward the right at the eight somite stage (approximately 22 to 23 days gestation).[67,68] During the next 10 to 12 days, while cardiac and great vessel septation is occurring, the apex of the heart gradually migrates from the right side of the thorax to its normal location in the left hemithorax. In situs solitus, dextrocardia has been explained as lack of this normal leftward migration of the cardiac mass.[69–71] De la Cruz, et al.[70,71] have suggested a similar left-to-right migration of the l-loop ventricles normally present in situs inversus. Extending this reasoning, they have attempted to explain the high incidence of atrioventricular discordance (l-loop ventricles) in individuals with situs solitus and dextrocardia as a consequence of the natural tendency of an l-loop heart to migrate into the right hemithorax.

Nomenclature and Classification

A variety of terms have been used to describe hearts in the right side of the chest, including dextroposition, dextroversion, dextrorotation, and isolated, genuine, mixed, pivotal, true, and mirror-image dextrocardia. Since these terms are difficult to remember and have been interpreted differently by several authors, it is preferable to avoid their use altogether. However, since some are

used widely, a brief description of the most common terminology is necessary for interpretation of the literature. The terms *dextroversion,*[32,39,40,72] *dextrorotation,*[42] and *pivotal dextrocardia*[26,40] generally are used to describe dextrocardia with situs solitus. The heart often appears as if the apex simply has been swung from the left side of the chest to the right. Isolated dextrocardia[36] has a similar connotation, implying that the other organs are in their normal location with respect to the body and that dextrocardia is an isolated finding. Dextroposition implies that the heart has been shifted rightward by external causes.[40,74] Mixed dextrocardia is a term used to indicate dextrocardia with atrioventricular discordance.[40,68,73] Mirror-image dextrocardia generally is applied to more-or-less normal hearts in subjects with situs inversus.

It is reasonable to consider separately those cases of dextrocardia that are due to displacement of the heart into the right hemithorax by external causes—pneumothorax, diaphragmatic hernia, or hypoplasia of the right lung—a condition sometimes referred to as secondary dextrocardia. The remaining hearts must be described in a segmental manner, as outlined above. The location of the other viscera is key since the presence of situs solitus, situs inversus, or heterotaxy have major implications in terms of the likelihood and type of intracardiac abnormalities. Thus, the simplest classification system is one that separates cases of secondary dextrocardia, then divides the remainder according to visceral situs (Table 75–2).

Clinical Evaluation

Although dextrocardia can be diagnosed by physical examination, most likely it is detected by chest roentgenography. The clinical presentation may be that of a newborn with cyanosis, respiratory distress, or a heart murmur. Occasionally, dextrocardia is detected on a chest roentgenogram performed as a screening test or evaluation for other medical disorders.[54,56,57] The incidence of congenital heart disease in secondary dextrocardia is not established. When dextrocardia is due to a simple mechanical factor such as pneumothorax, the incidence of heart disease is probably the same as that in the general population. Cases associated with other birth defects such as diaphragmatic hernia, however, may have a greater likelihood of intracardiac abnormalities. The incidence of congenital heart disease in primary dextrocardia varies from under 10% in situs inversus to over 90% in situs solitus (see below). In cases of secondary dextrocardia, the chest roentgenogram may be the only necessary diagnostic test. In the absence of such an obvious cause, the initial step in evaluation of dextrocardia is to determine the situs of the other viscera. Frequently, the chest roentgenogram is useful in illustrating the location of the liver and stomach. The situs of the lungs may be inferred from chest films.[1,27–29] Although somewhat overshadowed by modern imaging techniques, the electrocardiogram is often helpful in evaluation of dextrocardia: a "P" vector directed leftward and inferiorly suggests situs solitus of the atria, whereas a rightward "P" axis suggests situs inversus (Fig. 75–1). Nonsinus pacemakers are probably responsible for most exceptions to the rule.[75,76]

Table 75–2. Simplified Classification of Right-Sided Hearts

Primary
Situs inversus
Situs solitus
Heterotaxy
Secondary (pleural, chest wall, or pulmonary causes)

Many of the details of visceral situs and intracardiac anatomy can be determined by echocardiography.[47–50,77–81] A comprehensive examination should include identification of the abdominal viscera, systemic venous connections to the heart, the atrioventricular connection(s), ventricular anatomy, ventriculo–arterial connections, and the anatomy of the aortic arch and pulmonary arteries. Additionally, the presence of septal defects, valvular stenosis or insufficiency, and pulmonary venous connections may be determined. Additional hemodynamic and anatomic data may be obtained by cardiac catheterization and angiocardiography.[38–46]

Associated Cardiac Abnormalities

Situs Solitus. Dextrocardia in the presence of situs solitus is frequently, but not invariably associated with major intracardiac abnormalities. The literature is somewhat difficult to interpret, since dextrocardia with situs solitus has been called dextrorotation,[42] dextroversion,[32,39,40,82] isolated dextrocardia,[36] type II dextrocardia,[40] and type III dextrocardia.[35] Most angiocardiographic and autopsy studies have revealed a very high incidence of intracardiac anomalies.[18,21,32,40–46,73,83–86] The most common findings are summarized in Table 75–3. Atrioventricular discordance (l-loop ventricles) is a frequent finding, present in nearly half of cases. Over one-fifth of cases have single ventricle and the majority of the remainder have ventricular septal defect. Ventriculo–arterial discordance (transposition) is the most common relation of the great arteries. About half of cases described have atrioventricular discordance and ventriculo–arterial discordance, and thus the physiology of "corrected" transposition. Normally related great arteries are present in about 8%. Pulmonary stenosis or atresia is common (60%) and right aortic arch uncommon (4%).

Although the incidence of congenital heart disease is said to approach 100% among patients with situs solitus and dextrocardia,[53] this estimate, based largely on autopsy and angiocardiographic data, is probably too high. Scattered cases of situs solitus, dextrocardia, and normal intracardiac anatomy are reported in the literature[18,21,39,46]; presumably, many more are undetected in the absence of symptoms or cardiac murmurs. Some of these may be secondary to hypoplasia of the right lung (Fig. 75–2).

Scimitar syndrome: The scimitar syndrome is an uncommon but

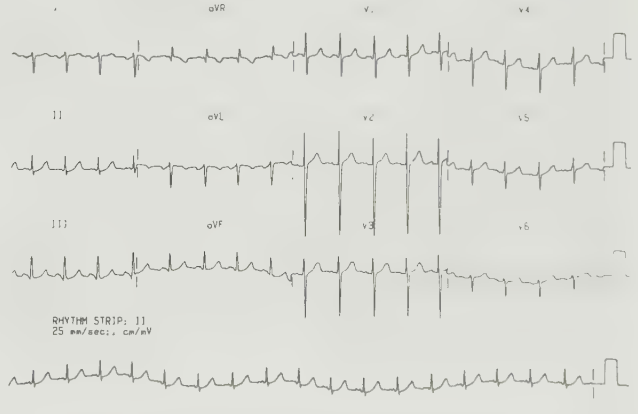


Fig. 75–1. Electrocardiogram from patient with dextrocardia and situs inversus. Note the negative waves in lead I and the progressively decreasing voltage in left chest leads.

Table 75–3. Intracardiac Abnormalities in Patients with Right-Sided Hearts Studied by Angiocardiography or Autopsy

	Dextrocardia with Situs Solitus	*Dextrocardia with Situs Inversus*
AV discordance	50%	25%
Single ventricle	25%	Uncommon
VSD	60%	60%
"Corrected" TGA	50%	20%
"Complete" TGA	10%	30%
DORV	10%	30%
NRGA	40%	40%
PS/PA	60%	50%
Right aortic arch	5%	80%

Note: Percentages listed are approximations based on 188 cases of dextrocardia with situs solitus[18,21,40,45,46,73,84] and 89 cases of dextrocardia with situs inversus.[18,21,40,46,84] Differences in terminology preclude a precise tabulation. Total for great artery configurations exceeds 100% because some reports did not consider TGA and DORV mutually exclusive diagnoses.

Key: AV = atrioventricular; DORV = double outlet right ventricle; NRGA = normally related great arteries; PS/PA = pulmonary stenosis or pulmonary atresia; and TGA = transposition of great arteries.

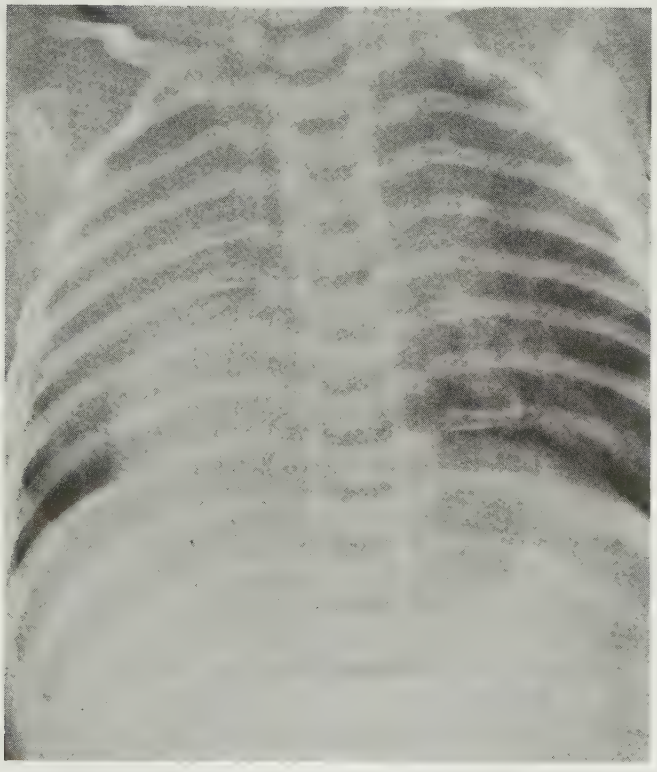


Fig. 75–2. Dextrocardia in a neonate with mild respiratory distress. Patient had situs solitus and normal intracardiac anatomy. Density in right hemithorax suggests atelectasis and/or hypoplasia of right lung.

well-described constellation of cardiopulmonary anomalies consisting of dextrocardia, situs solitus of the atria and viscera, hypoplasia of the right lung, anomalous systemic arterial blood supply to the right lung and anomalous pulmonary venous connection of the right lung to the inferior vena cava. The anomalous pulmonary vein is often visible on the chest roentgenogram as a curvilinear shadow in the right lung and resembles a Turkish sword or "scimitar" (Fig. 75–3).

There appear to be two relatively distinct clinical patterns of the scimitar syndrome: 1) infants with cyanosis, respiratory distress, and failure to thrive often with pulmonary hypertension and complex intracardiac defects[87–89]; and 2) a group of older children and adults who present with a heart murmur, recurrent pulmonary infection, or only an abnormal chest roentgenogram[90] (see Fig. 75–3). The latter group has a very favorable prognosis with or without surgery (right pneumonectomy). Approximately 40% of cases of scimitar syndrome diagnosed in childhood have associated intracardiac anomalies.[91–94]

Situs Inversus. The incidence of congenital heart disease in subjects with dextrocardia and situs inversus is much less than for dextrocardia and situs solitus, but precise determination is not available. Korth and Schmidt[83] reviewed 1000 cases of mirror-image dextrocardia with situs inversus and found congenital heart disease in only one (an incidence lower than that usually cited for the incidence of congenital heart disease in the general population).[63]

The consensus of opinion regarding the individual with situs inversus aptly was summarized by Cleveland[30] in 1926:

> He does not seem to be left handed more than his fellows. He is apt to live his life unmarked by any peculiarity and die of the same diseases that carry off the rest of mankind . . . The European case reports usually end with the observation that the individual was quite fit for military duty.

This picture of situs inversus is quite different from that depicted for patients with situs inversus who are referred to pediatric cardiology clinics[40–46,49,53,85] or described in autopsy series.[18,21,24–26] These studies all report a very high incidence of congenital heart disease obviously reflecting the reason for referral.

The types of cardiac abnormality found in dextrocardia with situs inversus are summarized in Table 75–3, and an example is illustrated in Figure 75–4. Atrioventricular discordance and transposition complexes are common, but less frequent than in dextrocardia with situs solitus. Physiologically complete forms of transposition are more common than so-called corrected forms. Double-outlet right ventricle, pulmonary stenosis or atresia, and ventricular septal defect are present in one-third to two-thirds of reported cases. The aortic arch is usually right-sided.

Although most patients with situs inversus have a normal heart, they are at greater risk for pulmonary diseases than the general population. The most notable of these is the so-called Kartagener syndrome. In 1933, Kartagener described four patients with situs inversus, chronic sinusitis, nasal polyposis, and bronchiectasis.[95] Subsequent studies by Kartagener[96] and others[55,97,98] suggested that the incidence of bronchiectasis among patients with situs inversus (15 to 25%) was higher than expected by chance. The ultrastructural basis for the respiratory disease and the male infertility in this syndrome subsequently was shown to be due to an abnormality of the dynein arms on the microtubules of the cilia and spermat-

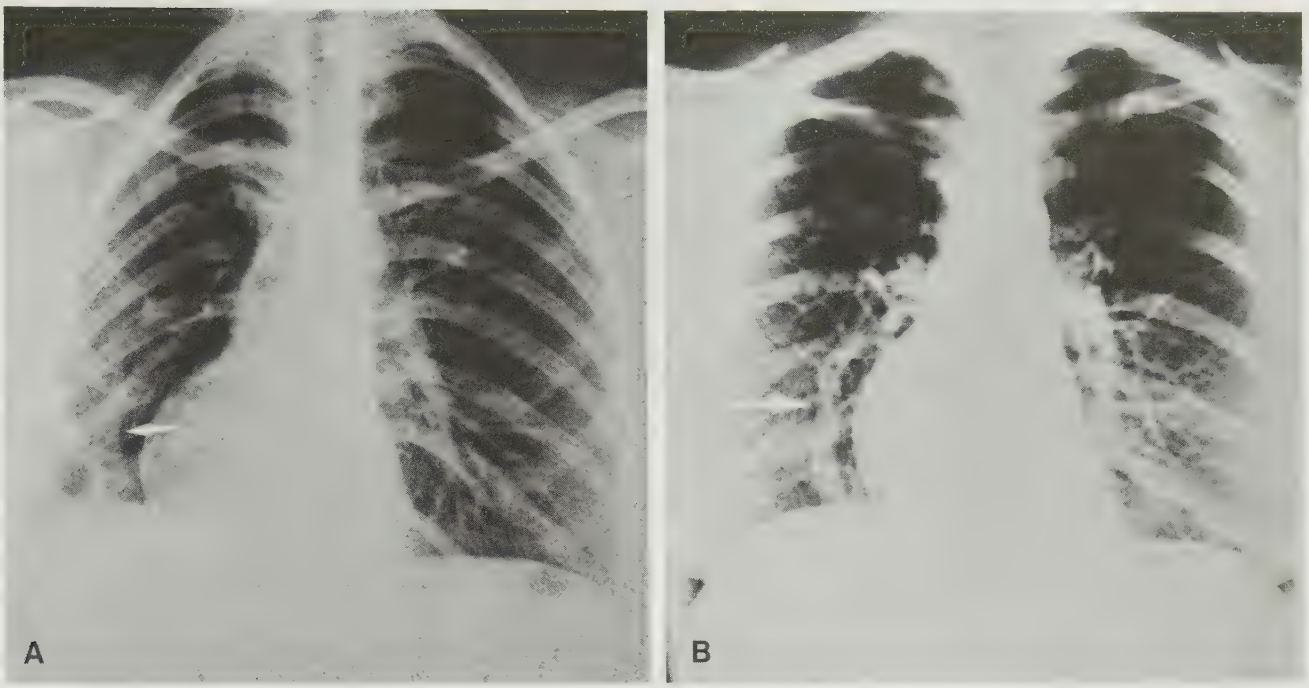


Fig. 75–3. Asymptomatic adults with dextrocardia and scimitar syndrome (A and B). Right pulmonary vein produces sword-shaped shadow (arrows) as it runs inferiorly toward diaphragm (especially well seen on the high-contrast film [B]). (Courtesy Drs. Peter Armstrong (A) and Paul Dee (B).)

ozoa, with resultant immotility of these structures and decreased mucociliary transport.[99–102]

Levocardia

Historic Aspects

Van Praagh[21] cites the reports of Martin,[103] and Breschet[104] as the first descriptions of isolated levocardia. The condition is quite rare and cases of isolated levocardia (in its simplest form, levocardia with situs inversus) often are included with descriptions of levocardia occurring in the asplenia/polysplenia syndromes.

Associated Cardiac Disease

Levocardia occurring in the presence of situs inversus or heterotaxy is almost invariably associated with major intracardiac anomalies[59,21,86,105–110] (Fig. 75–5). Of 65 autopsy cases reviewed by Van Praagh,[21] 9 were associated with situs inversus, and the remaining 56 had situs ambiguous. All 9 of the cases associated with situs inversus had D-ventricular loops and D-malposition of the aorta (two with double-outlet right ventricle). Thus, the physiology presumably resembled that of corrected transposition. Associated lesions included atrioventricular canal (6/9), total anomalous pulmonary venous connection (4/9), and pulmonary stenosis or atresia (8/9).

Thus, when the heart is left-sided but other viscera are not in their usual location: 1) the likelihood of intracardiac abnormalities is very high (close to 100%) and 2) the likelihood of either asplenia of polysplenia is high (about 80%).[25]

Mesocardia

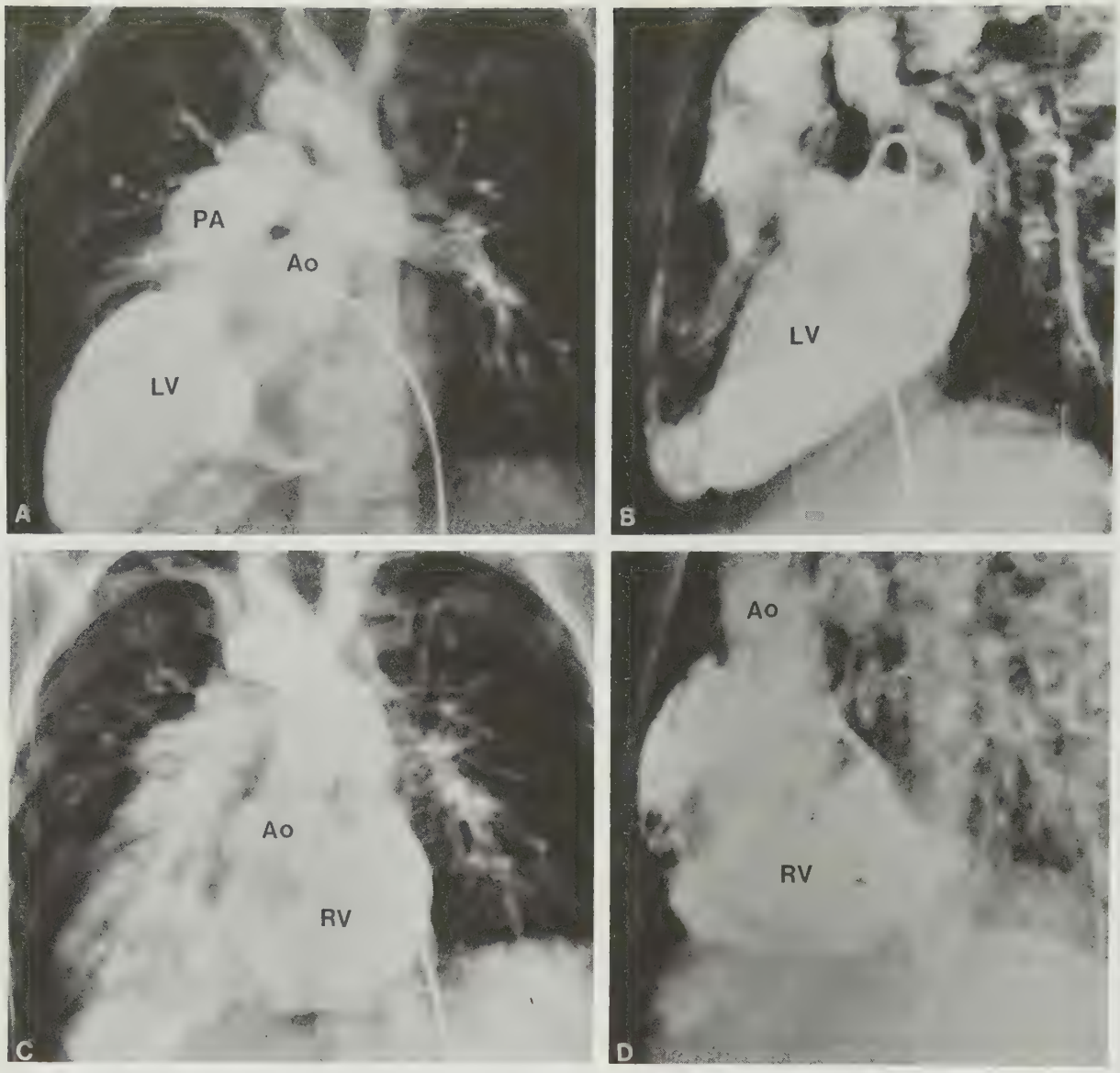
Mesocardia, defined as a midline heart that is in neither the left nor the right hemithorax, is either very rare or quite common, depending on the rigidity of the definition and the perspective of the beholder. Van Praagh[21] found mesocardia to be quite rare, occurring only in 0.2% of his *autopsied cases of congenital heart disease*. He analyzed 17 cases (4 of his own and 13 described by Lev[102]). Situs solitus was present in 12, situs inversus in 2, and situs ambiguous in 3. Normally related great arteries were found in 5 of these cases, corrected transposition in 3, and complete transposition in 2. Shaher[86] described five patients with mesocardia, all with situs solitus. Transposition was present in 2, patent ductus arteriosus in 2, ventricular septal defect in 1, and anomalous coronary artery in 1.

Clinicians viewing large numbers of chest roentgenograms have a somewhat different perspective. Many tall, slender adolescents and adults have an almost vertical heart, which might be termed *mesocardia*. As a result, some authors have suggested that mesocardia itself is of little or no consequence.[112,113] Thus, the setting in which it occurs is a much more important determinant of the likelihood of intracardiac abnormalities than the fact that the heart is in the midline; a cyanotic newborn with a murmur and a midline heart is quite likely to have serious heart disease whereas in an asymptomatic child with no murmur, a midline heart is probably of no concern (Fig. 75–6).

Summary

The following generalizations apply to hearts in abnormal locations with the thorax:

1. Dextrocardia with situs solitus (isolated dextrocardia) is almost always associated with intracardiac abnormalities, whereas atrioventricular discordance occurs with transposition of the great arteries the most common. The scimitar syndrome should be considered even in the absence of obvious intracardiac abnormalities.



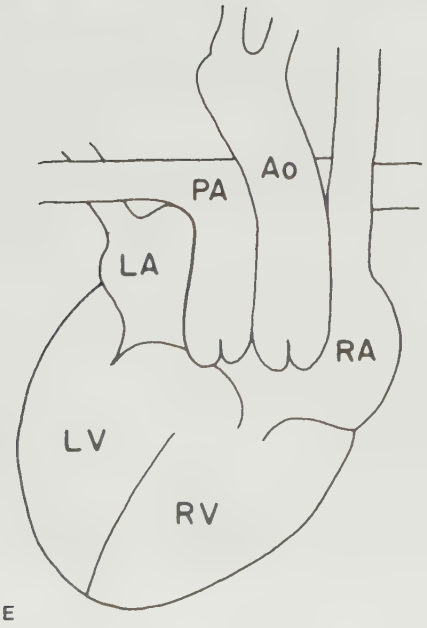


Fig. 75–4. Dextrocardia with situs inversus. From roentgenograms of the abdomen and from the course of the venous catheter, there is situs inversus of the viscera and atria. The right-sided ventricle has the morphology of a ''left'' ventricle (A and B) and the left-sided ventricle resembles a ''right'' ventricle (C and D). The great arteries are side by side, aorta to the left, and both arise from the anatomic right ventricle. As shown in (E), the anatomy may be summarized as dextrocardia, situs inversus of viscera and atria, atrioventricular concordance, and double outlet right ventricle (L-malposition of the aorta).

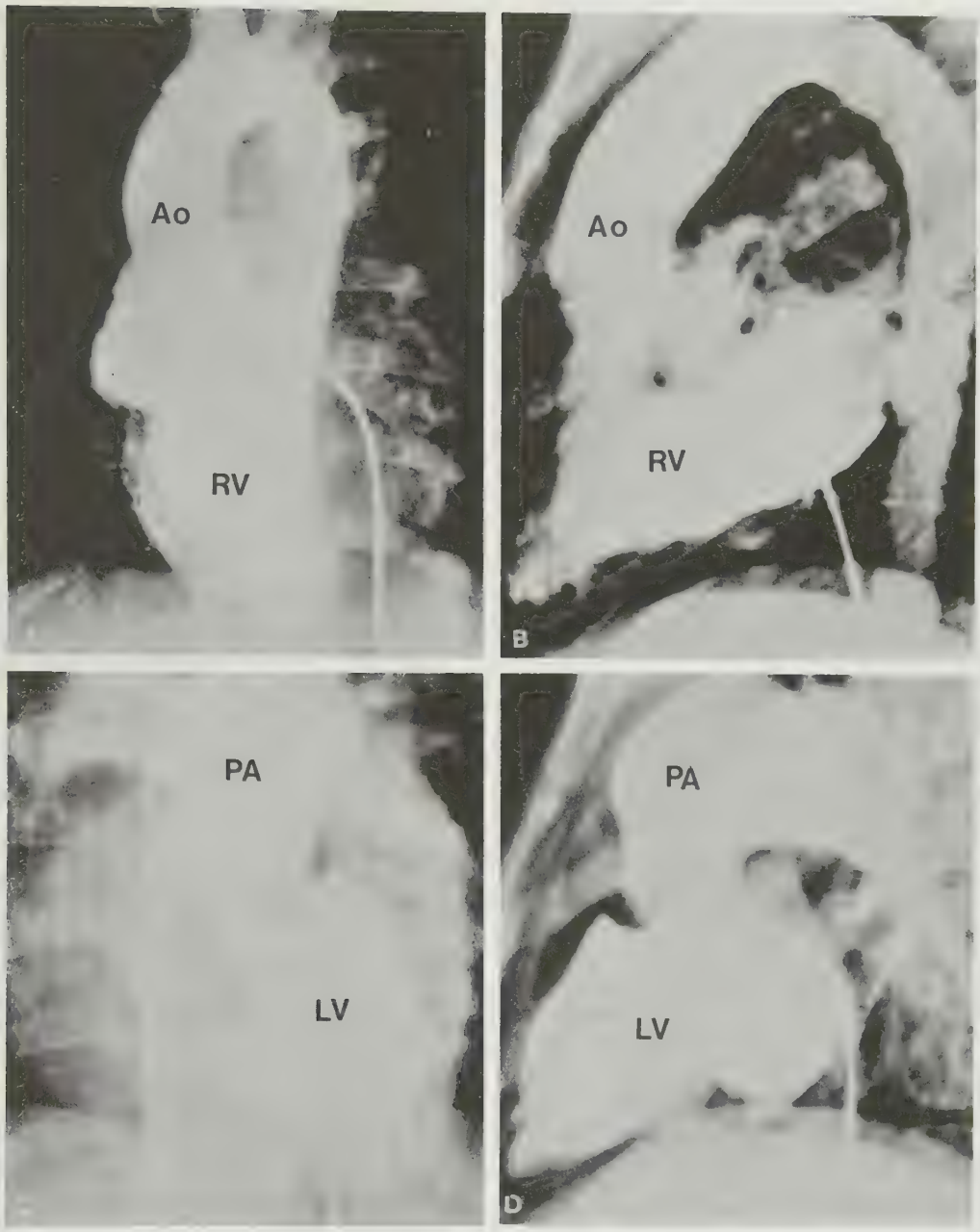


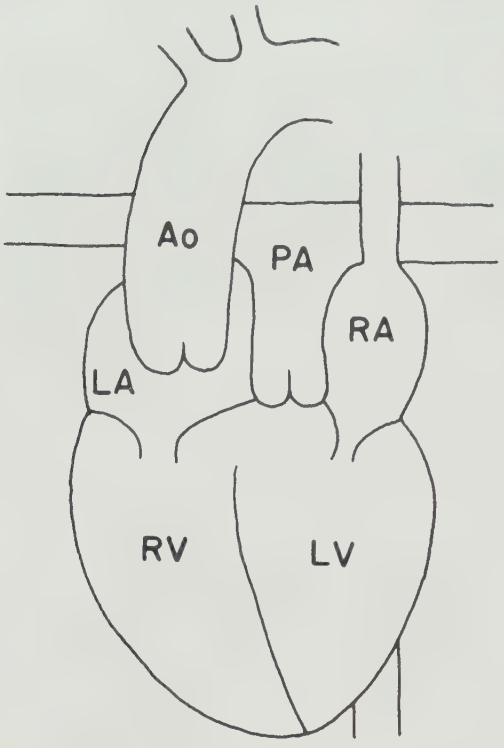
Fig. 75–5. Levocardia with situs inversus. Roentgenograms of the abdomen and the course of the venous catheter show situs inversus of the viscera and atria. The right-sided ventricle (A and B) has the morphology of a right ventricle and gives rise to the aorta. The left-sided ventricle (C and D) has left ventricular morphology and gives rise to the pulmonary artery.

2. In dextrocardia with situs inversus, the incidence of congenital heart disease is probably the same as in the general population, but it is much higher among those patients referred to cardiology clinics. The Kartagener syndrome is present in 15 to 25% of patients with situs inversus.
3. Isolated levocardia is almost invariably associated with major intracardiac abnormalities.
4. Approximately one-third of patients with dextrocardia and at least two-thirds of those with isolated levocardia have either asplenia or polysplenia.

HETEROTAXY

Definition

Unlike the orderly and predictable arrangements of the organs and blood vessels in situs solitus and situs inversus, those of the visceral heterotaxy syndromes appear random and disorderly. Thus, these conditions often are referred to as situs ambiguous or situs indeterminate. Within this group of conditions are two predominant patterns: those associated with asplenia and those associated with polysplenia. Individuals with asplenia frequently



E

Fig. 75–5 (cont.) As summarized in (E), there is levocardia, situs inversus of viscera and atria, atrioventricular discordance (d-loop), and transposition of the great arteries (complete transposition with d-malposition of the aorta).

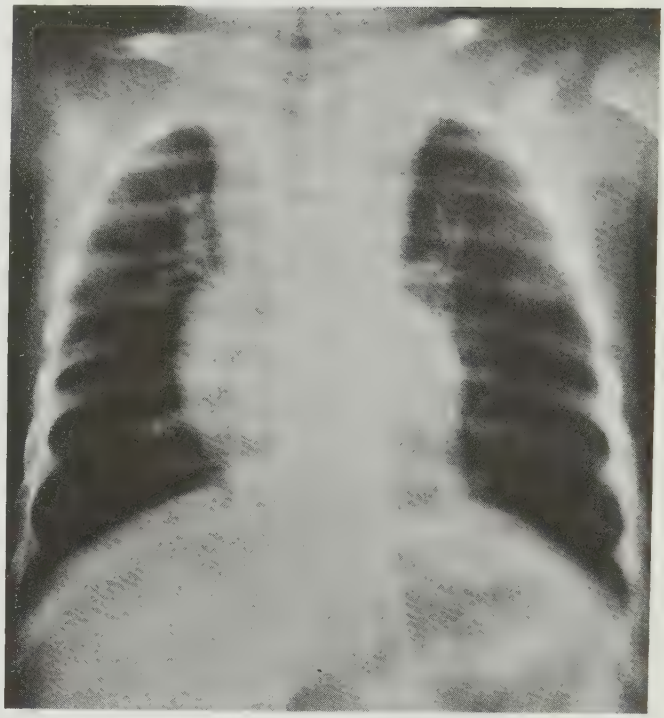


Fig. 75–6. Chest roentgenogram in an asymptomatic 2-month-old infant with a midline heart (''mesocardia''). Patient has situs solitus and normal intracardiac anatomy, illustrating that the presence of mesocardia itself does not necessarily indicate serious underlying congenital heart disease.

have internal viscera resembling bilateral right-sidedness whereas those with polysplenia frequently appear to have bilateral left-sidedness. Macartney et al.[8] have argued that these conditions should be termed right or left isomerism since the situs is not truly ambiguous and the presence or absence of the spleen is an inconstant variable. Freedom[104] concluded that these conditions represented abnormal persistence of normally symmetric embryonic structures rather than bilateral left- or right-sidedness. Nonetheless, the terms *asplenia syndrome* and *polysplenia syndrome* are used widely and provide a simple memory aid for understanding the conditions. (It is easy to remember that an individual with two right sides would have no spleen and one with two left sides might have several spleens.)

The two conditions thus are discussed below as separate syndromes (not specific malformations or diseases) of commonly occurring constellations of visceral and cardiac abnormalities.

Historical Aspects

Although congenital absence of the spleen has been recognized for over 200 years,[115] it was not until the 1950s and the publication of several large series of autopsied cases of asplenia[115–117] that there was an appreciation of the almost-invariable presence of a specific set of cardiovascular abnormalities in patients born without a spleen. As a result of his exhaustive treatise on the subject,[117] Ivemark's name has been associated with the constellation of cardiac malformations associated with asplenia: ''the Ivemark syndrome.'' Ivemark called attention to the appearance of bilateral right-sidedness in asplenia and bilateral left-sidedness in polysplenia, findings subsequently reiterated by others.[2,118–121]

Incidence, Etiology, and Genetics

The heterotaxy syndromes, while not common in the general population, are by no means rare, especially in tertiary care centers with neonatal intensive care units. The asplenia/polysplenia syndrome is present in 3% of neonates with structural heart disease[122] and in 30% of patients dying with cardiac malposition.[21]

The etiology of the heterotaxy syndromes is undetermined. As just described, Layton's hypothesis[64–66] of a lack of normal genetic control leading to random organization of viscera is an appealing theory that would explain many aspects of cardiac malposition and heterotaxy. Other factors that have been proposed as causes of asplenia syndrome include: 1) vascular disturbances resulting in agenesis of the spleen[115]; 2) failure of the splenic artery to reach the developing spleen[123]; 3) abnormal embryonic body curvature.[124]

The familial clustering of cases of situs inversus, asplenia, and polysplenia suggests a common genetic basis.[125–126] In reviewing the genetics of these conditions, Niikawa et al.[125] found reports of eight families with two or three sibs with asplenia; four sibships with two to four sibs with polysplenia; two brothers, one with situs inversus and one with asplenia syndrome, born to consanguineous parents; and two sibships where one sib had asplenia and one had polysplenia. Nukawa et al.[125] described a family in which a father with situs inversus totalis had one child with asplenia syndrome and another with polysplenia syndrome. Schidlow et al.[127] have described a sibship in which one side had Kar-

tagener syndrome and another polysplenia syndrome; both had abnormal respiratory cilia.

Embryology

Heterotaxy obviously is not a specific disease but a constellation of cardiac, vascular, and visceral abnormalities. The embryology of many of the specific cardiovascular abnormalities is discussed in the chapters dealing with these malformations.

The major events in normal cardiac development that appear to be arrested or lacking in the hearts of patients with the heterotaxy syndromes occur largely during the fifth week of gestation.[67,68,128] During this week, the cardiac tube (already bent toward the right or left) undergoes septation. The growth of the endocardial cushions, septation of the conotruncus, lobation of the lungs, and rotation of the gut begin between the 28th and 35th gestational day. The connection between the roof of the left atrium and the pulmonary venous plexus is established by 30 to 32 days.[129] The spleen, which arises from the left side of the dorsal mesogastrium, is present histologically in 7.5- to 8-mm embryos (about 32 days) and is well demarcated in 13.5-mm embryos (35 to 36 days).

The hearts of many patients with either asplenia or polysplenia bear a rather striking resemblance to the heart of a normal embryo of about 35 weeks gestation. This has led to the suggestion that the asplenia syndrome results from a teratogenic insult in the fifth week of gestation,[115,131] although a more fundamental defect with a genetic basis seems more plausible.

Asplenia Syndrome

Clinical Features

The usual presentation is in a cyanotic male newborn, often with respiratory distress. The first and second heart sounds are single (and, since dextrocardia is common, the heart sounds may be heard better over the right hemithorax). There may be an ejection systolic murmur, a continuous murmur, or no murmur. A midline liver often is identifiable by palpation.

Clues to the presence of the asplenia syndrome are often present on the chest roentgenogram[132,133] (Figs. 75–7 and 75–8), and this condition should be considered when the cardiac position is discordant with that of the stomach and liver, especially if pulmonary vascular markings are very diminished (due to pulmonary atresia) or there is pulmonary edema (obstructed pulmonary veins) (see Fig. 75–8).

The electrocardiogram is generally abnormal, but the findings are not specific for asplenia. The P wave axis may be either leftward and inferior (normal) or rightward and inferior,[134,135] or both, because of the frequency of bilateral sinus nodes.[121,136] Two atrioventricular nodes may be present.[136] Congenital complete AV block occasionally is present[137] and was diagnosed prenatally in the patient depicted in Figure 75–9. The frontal plane QRS axis and morphology reflect the cardiac position and intracardiac anatomy; the frontal plane QRS axis tends to be superior in the presence of two ventricles and inferior when there is a single ventricle.[138] The precordial leads may suggest left, right, or biventricular hypertrophy.[138]

The details of intracardiac anatomy and systemic and pulmonary venous connections can be established by two-dimensional echocardiography.[78] A transverse abdominal scan in a plane just inferior to the diaphragm is a useful starting point (see Fig. 75–8C). This

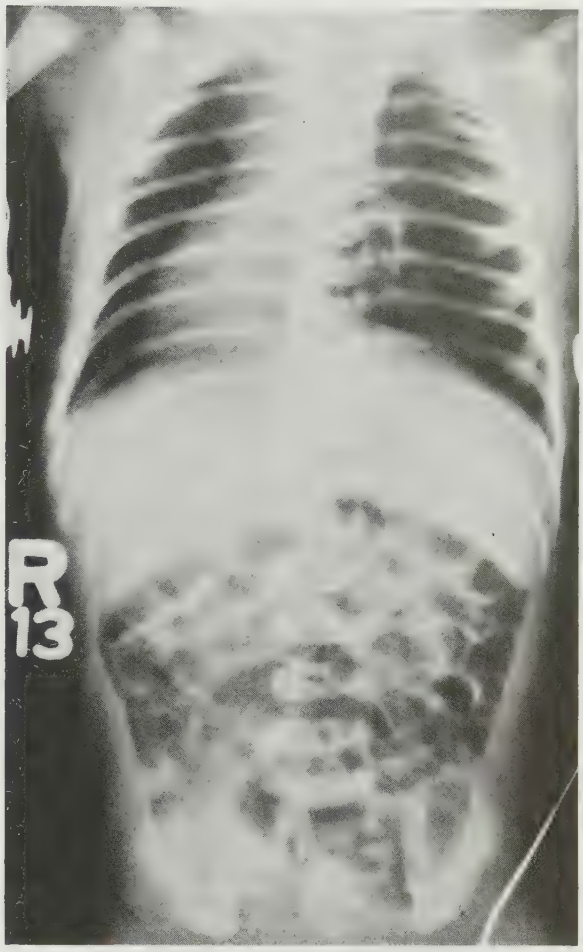
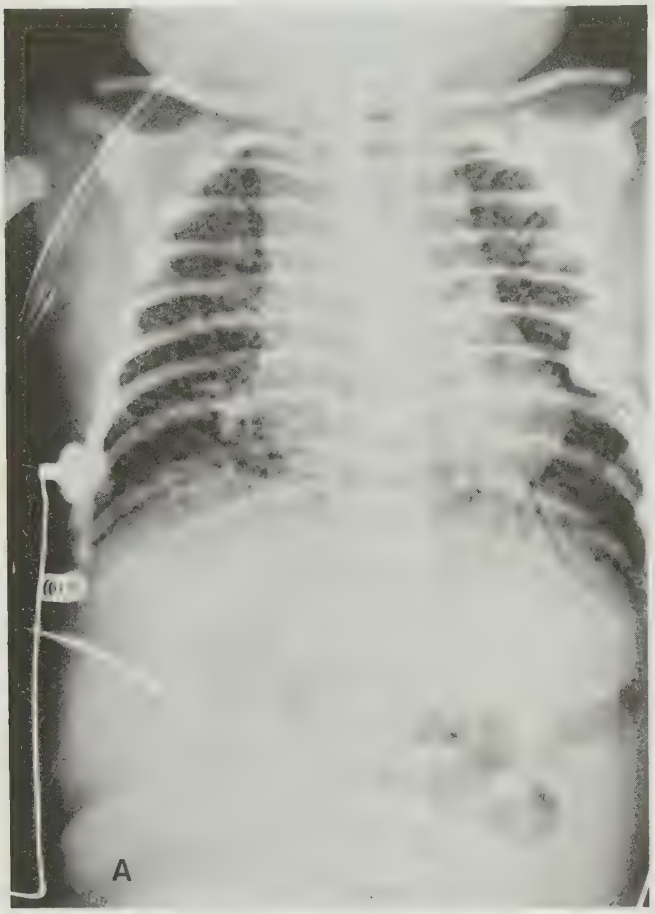


Fig. 75–7. One-day-old infant with dextrocardia and heterotaxy. Note stomach on left and large midline liver. Patient had atrioventricular canal, transposition of the great arteries, and pulmonary atresia. Autopsy demonstrated asplenia.

establishes the location of the liver, the inferior vena cava (if present) and the abdominal aorta. A subcostal four-chamber view will illustrate the location of the heart within the chest, the location of the cardiac apex, and the details of intracardiac anatomy (see Fig. 75–8). Because of the high incidence of total anomalous pulmonary venous connection, particular care is needed to determine the route of pulmonary venous return (see Fig. 75–8D).

Additional anatomic and physiologic information, if required, can be obtained from cardiac catheterization and angiocardiography (Fig. 75–10). These studies are particularly useful to document the presence of pulmonary venous obstruction, although catheterization of the pulmonary arteries may be difficult, or impossible, because of the presence of pulmonary stenosis or atresia.

Documentation of the absence of the spleen is more difficult than the confirmation of its presence. The presence of Howell-Jolly bodies in the red blood cells in a peripheral blood smear strongly suggests asplenia,[139,140] although they are occasionally present in normal infants in the first week of life.[141] Absence of the spleen can be inferred from the inability to demonstrate its presence by ultrasonography,[52,53] computed tomography,[52,53,142] or radionuclide scans.[143–145] But there have been no prospective stud-



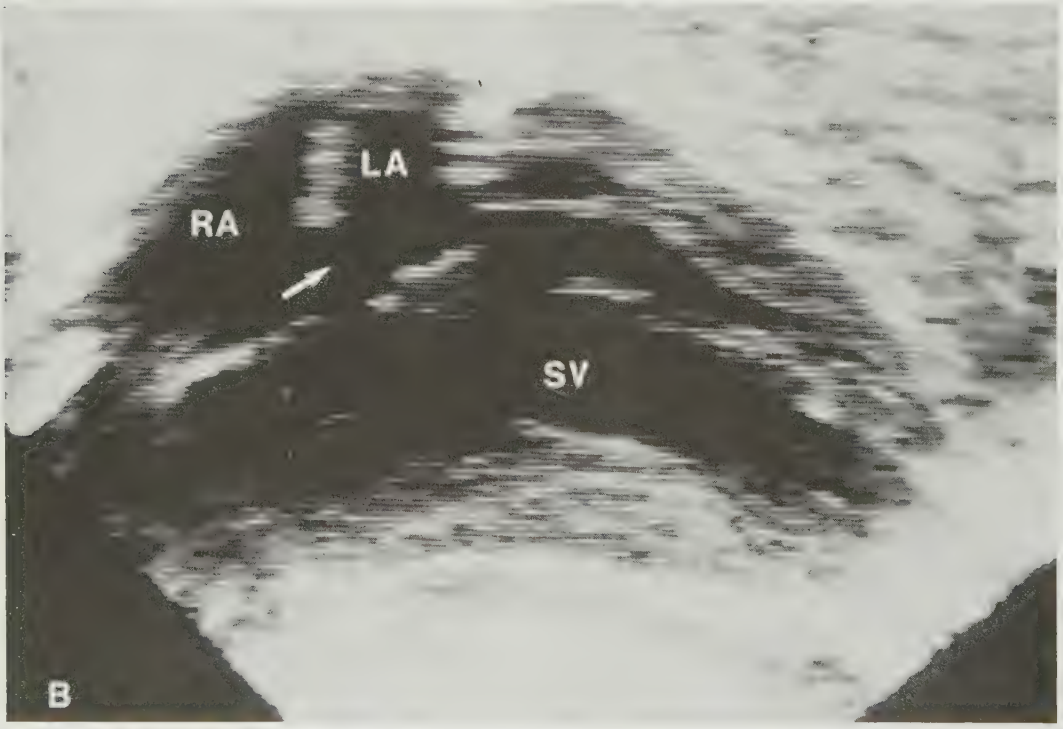


Fig. 75–8. Chest roentgenogram (A) and echocardiogram in cyanotic neonate with asplenia. The chest roentgenogram reveals pulmonary edema with a left-sided heart and right-sided stomach (note nasogastric tube). Subcostal four-chamber view of echocardiogram (B) demonstrates an ostum primum-type atrial septal defect (arrow), a common atrioventricular valve, and a single ventricle (SV). The aorta (not pictured) was anteriorly located; the pulmonary valve was atretic.

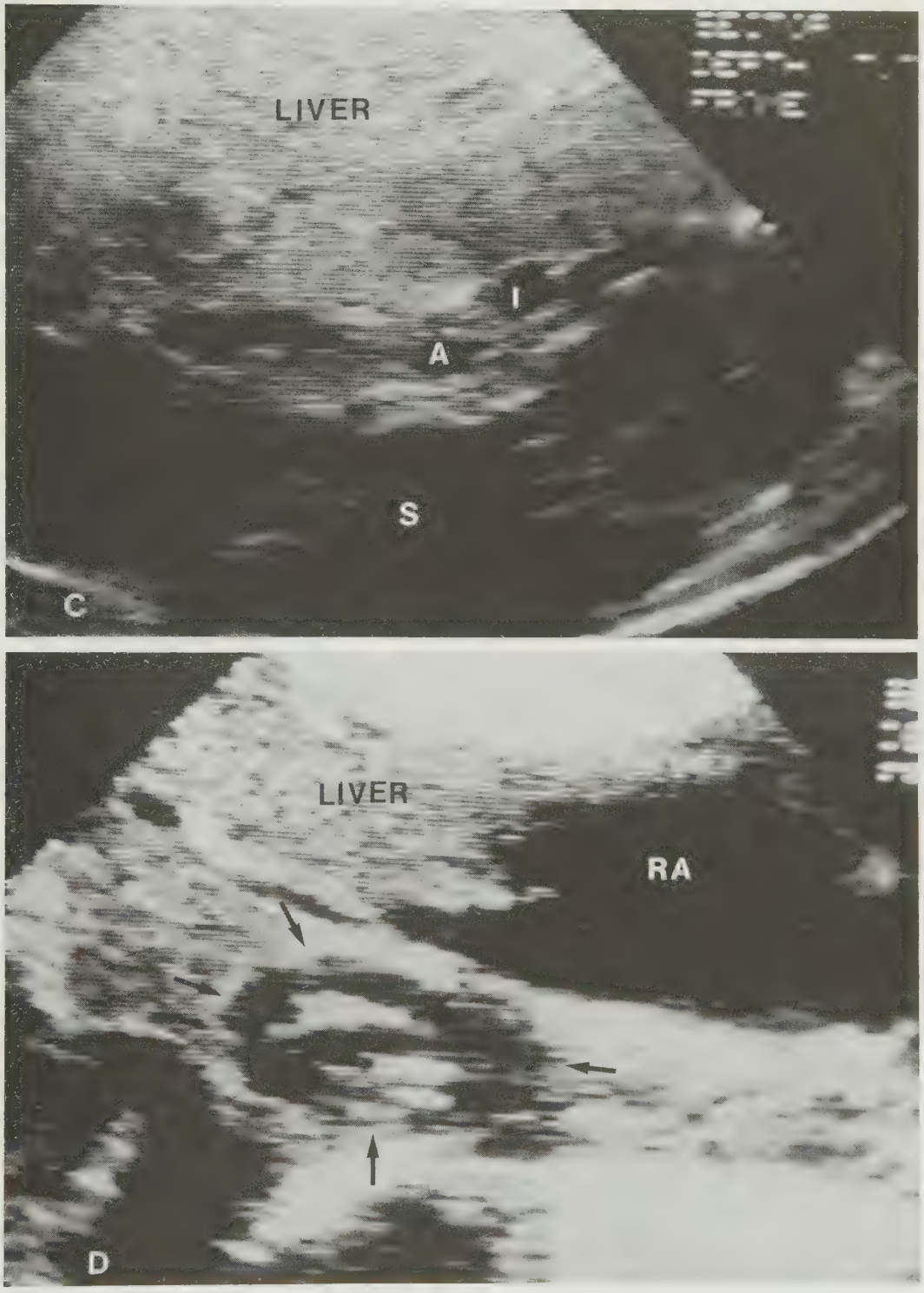


Fig. 75–8 (cont.) A transverse ultrasonic scan (C) just below the diaphragm shows the abdominal aorta (A) and inferior vena cava (I) juxtaposed on the left side of the spine (S). A parasagittal scan (D) reveals a vascular plexus (arrows) where the common pulmonary vein joins the portal system beneath the liver. RA = right atrium, LA = left atrium.

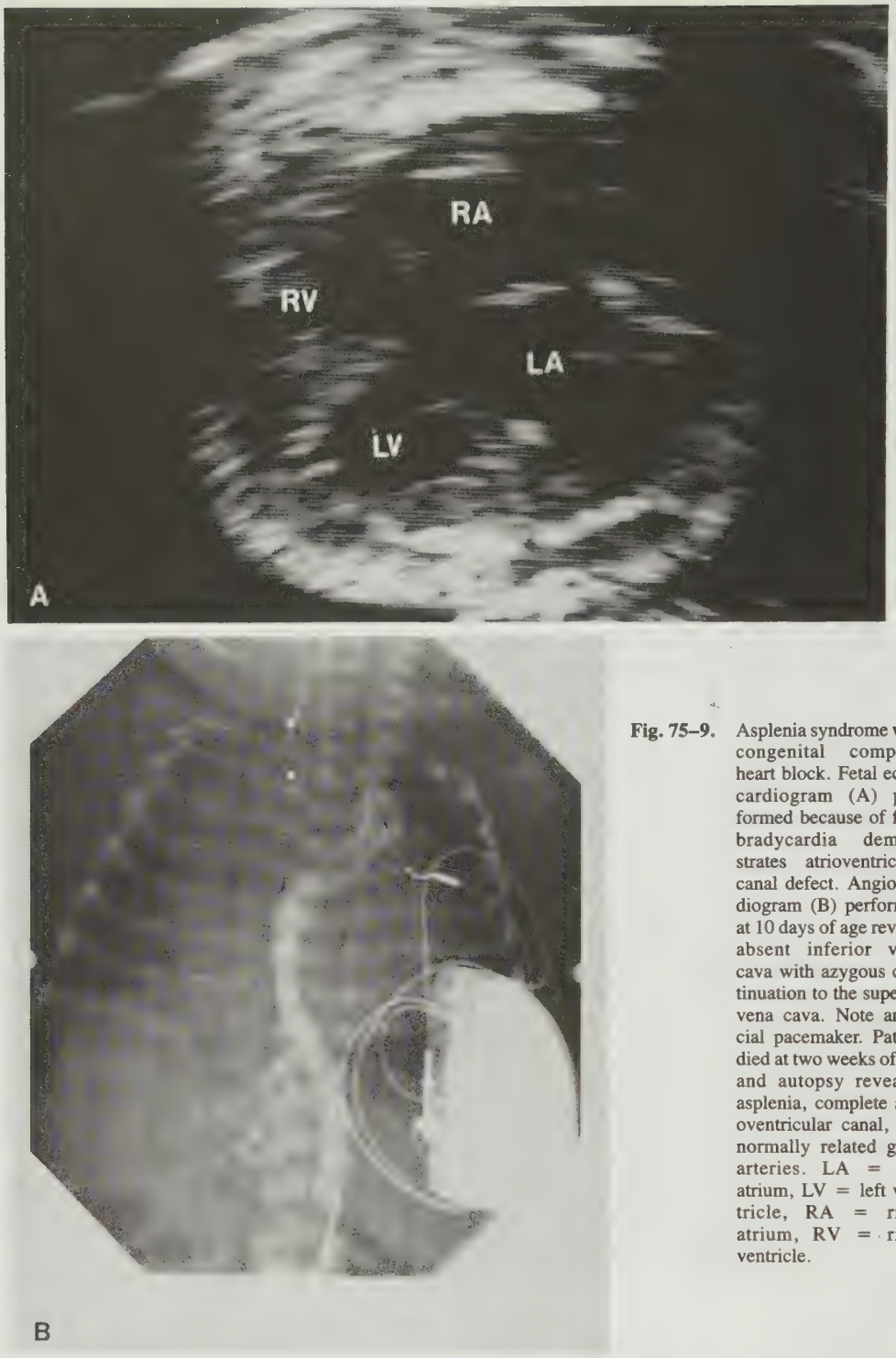


Fig. 75–9. Asplenia syndrome with congenital complete heart block. Fetal echocardiogram (A) performed because of fetal bradycardia demonstrates atrioventricular canal defect. Angiocardiogram (B) performed at 10 days of age reveals absent inferior vena cava with azygous continuation to the superior vena cava. Note artificial pacemaker. Patient died at two weeks of age and autopsy revealed asplenia, complete atrioventricular canal, and normally related great arteries. LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle.

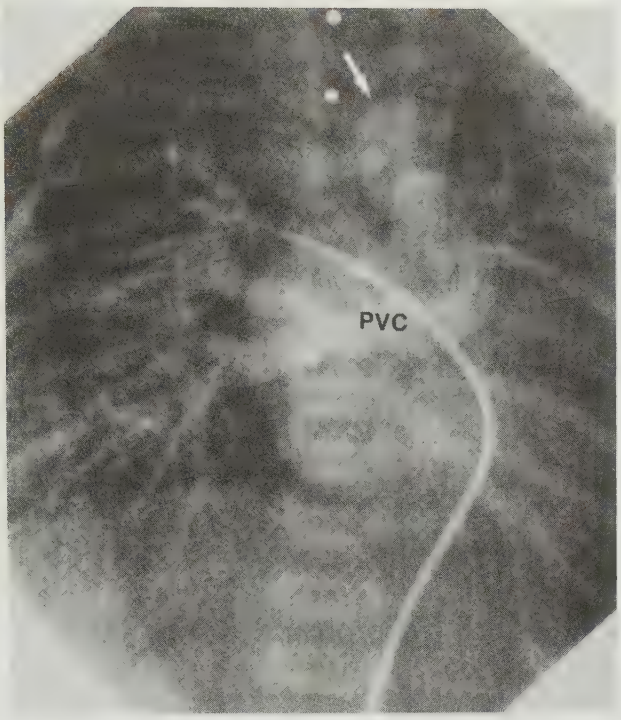


Fig. 75–10. Venous phase of pulmonary arteriogram in 6-week-old infant with asplenia syndrome. The pulmonary venous confluence (PVC) drains superiorly and enters the right superior vena cava (arrow). Pulmonary venous obstruction at this site produced severe pulmonary hypertension. The patient died at 3 months of age; autopsy revealed complete atrioventricular canal defect and transposition of the great arteries. The right lung had two lobes and the left had three lobes.

ies of the specificity or sensitivity of these techniques in proving asplenia. In clinical practice, asplenia often is assumed when features of right isomerism are present (in particular, radiographic features of right pulmonary isomerism), coupled with a complex intracardiac lesion and the presence of the inferior vena cava and abdominal aorta on the same side of the spine.[146]

Associated Cardiovascular Abnormalities

The typical cardiovascular anomalies are listed in Table 75–4. Atrioventricular canal, transposition (at least in the sense of an anterior aorta), and pulmonary stenosis or atresia are almost invariable features. At least 75% of cases have total anomalous pulmonary venous connection. A high percentage of cases (but not all) have right pulmonary isomerism. The presence of an inferior vena cava and abdominal aorta on the same side of the spine is nearly pathognomonic for asplenia,[146] although there are exceptions to this finding as well (Fig. 75–11). Left heart obstructive lesions, including aortic atresia have been reported[114,153,154] but are uncommon.

Immunologic Status

The role of the spleen in combatting infection, particularly from encapsulated organisms, is well-recognized. Thus, it is not surprising that patients with asplenia are particularly susceptible to overwhelming bacterial infection. In a review of cases of congenital asplenia at the Boston Children's Hospital, Waldman et al.[155] found that after the first month of life, patients with asplenia syndrome were at greater risk of dying from infection than from their heart disease. Older children with asplenia syndrome may also have deficiencies of IgM and IgE and suboptimal responses to pneumococcal vaccine.[156] Thus, in patients whose cardiac disease suggests asplenia syndrome, appropriate studies (hematologic, ultrasonic, radionuclide) should be performed to demonstrate the presence or absence of a spleen. If asplenia is documented or strongly suspected, the patient should receive prophylactic antibiotics. In the first six months of life, coverage against gram-negative and gram-positive organisms is recommended and ampicillin is used most commonly. Penicillin alone generally is sufficient for older infants and children. Administration of pneumococcal and hemophilus influenza vaccines likewise are recommended, with serologic testing to confirm an adequate response.[156]

Table 75–4. Incidence of Cardiovascular Abnormalities in the Asplenia and Polysplenia Syndromes

	Asplenia	*Polysplenia*
Dextrocardia	40%	40%
ASD/common atrium	90%	80%
Single ventricle	50%	10%
AV canal	85%	40%
TGA	80%	30%
PS/PA	80%	30%
LVOTO	Rare	40%
Bilat SVC	50%	40%
Absent IVC	Rare	70%
TAPVC	70%	Rare
PAPVC	Rare	40%
Right pulmonary isomerism	70%	10%
Left pulmonary isomerism	Rare	60%

Note: Percentages listed are approximations based on 300 cases of asplenia[2,21,124,131,138,150,151] and 247 cases of polysplenia.[2,21,150–152] Differences in terminology preclude precise numerical tabulation.

Key: ASD = atrial septal defect, AV canal = atrioventricular canal; TGA = transposition of the great arteries; PS/PA = pulmonary stenosis or atresia; LVOTO = left ventricular outflow tract obstruction; SVC = superior vena cava; IVC = inferior vena cava; TAPVC = total anomalous pulmonary venous connection; and PAPVC = partial anomalous pulmonary venous connection.

Management and Prognosis

The most common presentation of the asplenia syndrome is that of an intensely cyanotic neonate with a complex intracardiac lesion consisting of atrioventricular canal, transposition of the great arteries, and pulmonary stenosis or atresia. Initially, survival is often dependent upon creation of a systemic-to-pulmonary anastomosis to increase pulmonary blood flow. Management is complicated by the presence of an obstructed total anomalous pulmonary venous connection in many patients, often obscured by the diminished pulmonary blood flow pre-operatively. These patients may progress from intense cyanosis before a systemic-to-pulmonary anastomosis to severe pulmonary edema afterward due to the obstructed total anomalous pulmonary venous connection. Freedom et al.[157] have used a prostaglandin infusion to unmask venous obstruction pre-operatively.

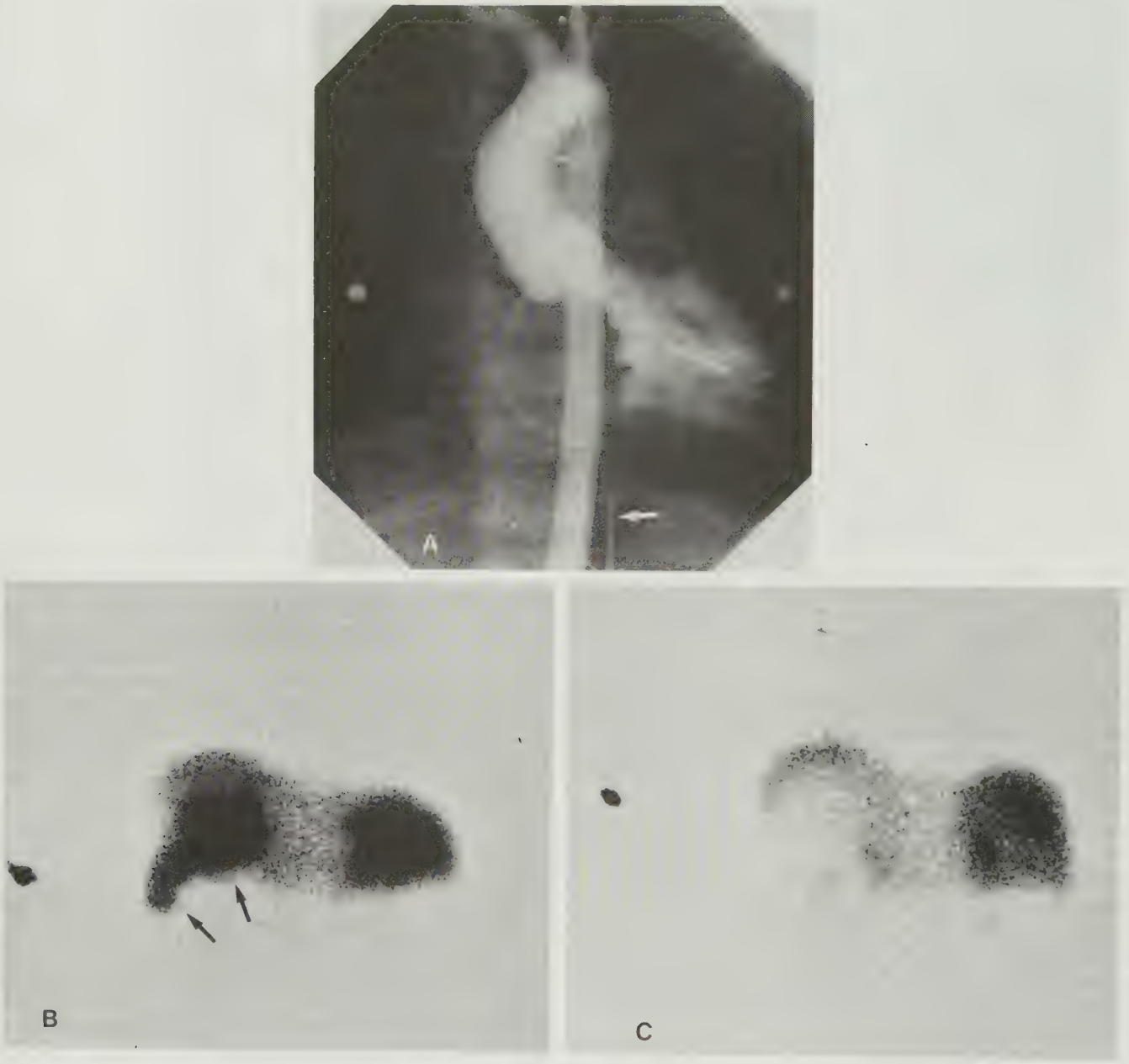


Fig. 75–11. Angiocardiogram (A), Tc^{99m} sulfur colloid liver/spleen scan (B), and Tc^{99m} disofenin (hepato-biliary) scan (C) in a 4-year-old boy with partial atrioventricular canal defect (common atrium) and situs inversus of the abdominal viscera. Left ventricular angiocardiogram reveals intact ventricular septum and the typical "scalloped" appearance of the left atrioventricular valve. Note that both the catheter in the inferior vena cava (arrow) and the abdominal aorta are on the left side of the spine. The sulfur colloid liver spleen scan reveals a left-sided liver and an additional irregular mass (arrows) in the right upper quadrant. Failure to visualize this mass on the hepato-biliary scan (C) suggests that it is splenic tissue (probably polysplenia). (Radionuclide scans courtesy of Dr. C.D. Teates.)

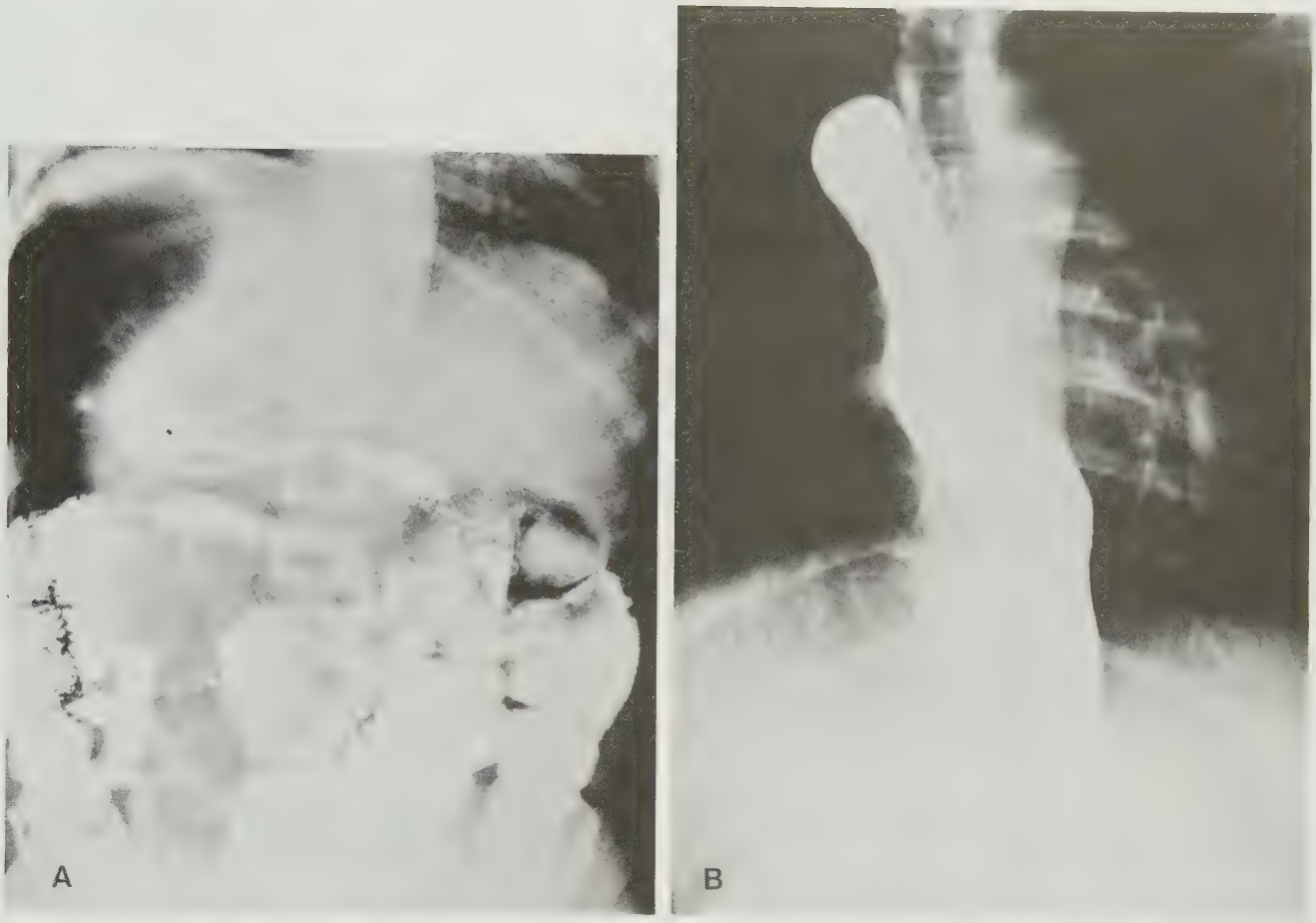


Fig. 75–12. Heterotaxia with azygous continuation of the inferior vena cava in an asymptomatic 35-year-old woman. Barium swallow (A) reveals stomach on right, liver on left, with malrotation of bowel. Venous angiogram (B) demonstrates azygous vein, which is on left side in abdomen, crosses to right at level of the diaphragm, and joins superior vena cava in the mediastinum. Heart is left-sided, and intracardiac anatomy was normal. Polysplenia is a diagnostic consideration but its confirmation was not undertaken.

Theoretically, the cardiac anomalies typical of the asplenia syndrome are amenable to intracardiac repair using modifications of the Fontan technique[158–161] or intricate intra- and extracardiac baffles.[161,162] The operative mortality is substantially higher in heterotaxy than in tricuspid atresia or single ventricle and is higher in patients with asplenia than in those with polysplenia.[159]

In view of the complexity of the intracardiac lesions and the decreased immune function, it is not surprising that the prognosis for infants with asplenia syndrome is poor. The mortality rate for typical asplenia syndrome approaches 80% in the first year of life.[2,150] One-year survival rates for "heterotaxy" (probably more heavily weighted by asplenia than polysplenia) were 43 and 54% at the Boston Children's Hospital[163] and the Texas Children's Hospital,[164] respectively, despite medical and surgical therapy. Exceptions have been reported,[165] and one patient known to many of the authors of this text died at Texas Children's Hospital at 32 years of age.

Polysplenia Syndrome

Clinical Features

There is much more variability in the presentation of patients with polysplenia than in those with asplenia. Since pulmonary stenosis and transposition are relatively infrequent, cyanosis usually is not severe and symptoms of congestive heart failure from large left-to-right shunts predominate. Other patients may be asymptomatic and a substantial number of patients may have no cardiac disease at all (Fig. 75–12). Several reports have described associated gastrointestinal anomalies, particularly extrahepatic biliary atresia.[166–168]

The findings on physical examination are not specific for polysplenia and reflect the associated cardiac abnormalities (see Table 75–4).

The chest roentgenogram may suggest the presence of the polysplenia syndrome (Fig. 75–13). Absence of the hepatic portion of the inferior vena cava with azygous continuation, a common feature in polysplenia, can be predicted from the presence of mediastinal "knuckle" (where the azygous vein joins the superior vena cava) (see Fig. 75–12A) especially when coupled with absence of the normal inferior vena cava shadow on the lateral view,[169,170] although the reliability of the latter finding has been questioned.[171]

Especially if it is suggestive of left pulmonary isomerism, bronchial symmetry is a more specific finding. Cardiac malposition or discordance between the cardiac apex and the stomach suggest

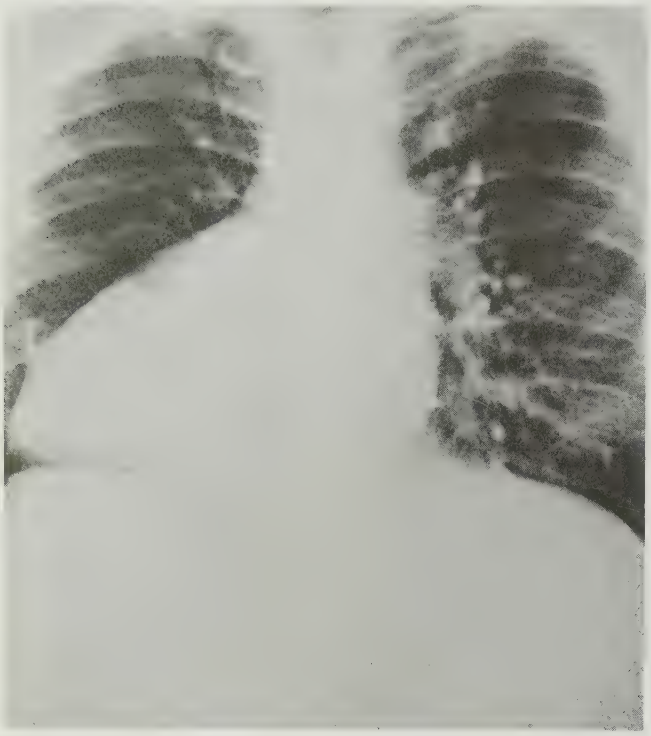


Fig. 75–13. Dextrocardia in an adult with polysplenia. Patient died of arrhythmia at 41 years of age. Autopsy demonstrated left pulmonary isomerism, complete atrioventricular canal, pulmonary stenosis, and transposition of the great arteries. A Blalock-Taussig anastomosis and a pulmonary valvotomy had been performed in early childhood.

heterotaxy in general, but are not particularly useful in distinguishing polysplenia from asplenia.

Electrocardiographic abnormalities are common in polysplenia. Since the sinus node is a right atrial structure, it is not surprising that left atrial isomerism is characterized by an absent, displaced, or hypoplastic sinus node.[136] As a result, the frontal plane P vector typically is oriented leftward and superiorly.[134–136,172,173] The course of the conduction system is abnormal,[136,174] and congenital complete AV block is present occasionally.[135,175] The QRS axis and precordial leads reflect 1) the position of the heart in thorax and 2) the nature of the intracardiac lesions. A superiorly oriented frontal plane QRS axis reflecting atrioventricular canal defect is a common finding.[136]

Many of the cardiac, great vessel, and visceral abnormalities associated with polysplenia can be demonstrated by echocardiography.[78,176,177] Although one would like to demonstrate anatomic features of left atrial isomerism, the atrial appendages generally cannot be imaged by echocardiography in sufficient detail to make this determination. In practice, the presence of polysplenia has been inferred from the absence of the hepatic portion of the inferior vena cava with azygous continuation. This vascular anomaly also may occur in the asplenia syndrome, but the latter can be excluded by sonographic demonstration of splenic tissue. (Fig. 75–14).

Ideally, the diagnosis of polysplenia (as opposed to heterotaxy in general or left isomerism) would be made by demonstration of multiple spleens. This can be accomplished in some patients by radionuclide scans,[143,144] although it may be difficult to distinguish two closely related spleens from one large spleen (see Fig. 75–11). The technique is more valuable to prove the presence of some splenic tissue (and thus exclude asplenia) than to diagnose polysplenia itself. More recently, computed tomography has been used to demonstrate the presence of multiple spleens[53,178] (Fig. 75–15). Visceral arteriography can be used to demonstrate polysplenia,[177] but this technique largely has been replaced by less invasive methods.

Associated Cardiovascular Abnormalities

The intracardiac and vascular abnormalities occurring in polysplenia syndrome are summarized in Table 75–4. Although there is considerable overlap, certain features occur with much higher frequency in either asplenia or polysplenia, fostering the notion that these conditions represent "syndromes." Atrioventricular canal defect is common to both conditions. In polysplenia, absence of the hepatic portion of the inferior vena cava is very common, as is partial anomalous pulmonary venous connection. Pulmonary stenosis or atresia is uncommon in polysplenia and, normally, related great arteries are more common than transposition. Left-sided obstructive lesions occur more frequently in the polysplenia syndrome than with asplenia.

Management and Prognosis

Many of the cardiac abnormalities associated with polysplenia are amenable to surgical correction, with low mortality. In some children with polysplenia, splenic function may not be normal; therefore, functional tests (e.g., Howell-Jolly bodies) should be performed in these patients as well.

There is a general perception that the prognosis in polysplenia is better than that for asplenia,[2,152,180] although in either case the prognosis is largely determined by the intracardiac anomalies. Rose et al.[150] found low one-year survival rates among infants with asplenia (21%) and those with polysplenia (39%). However, some individuals with polysplenia have minor cardiac abnormalities[152,181] and presumably have a normal or near-normal life expectancy.

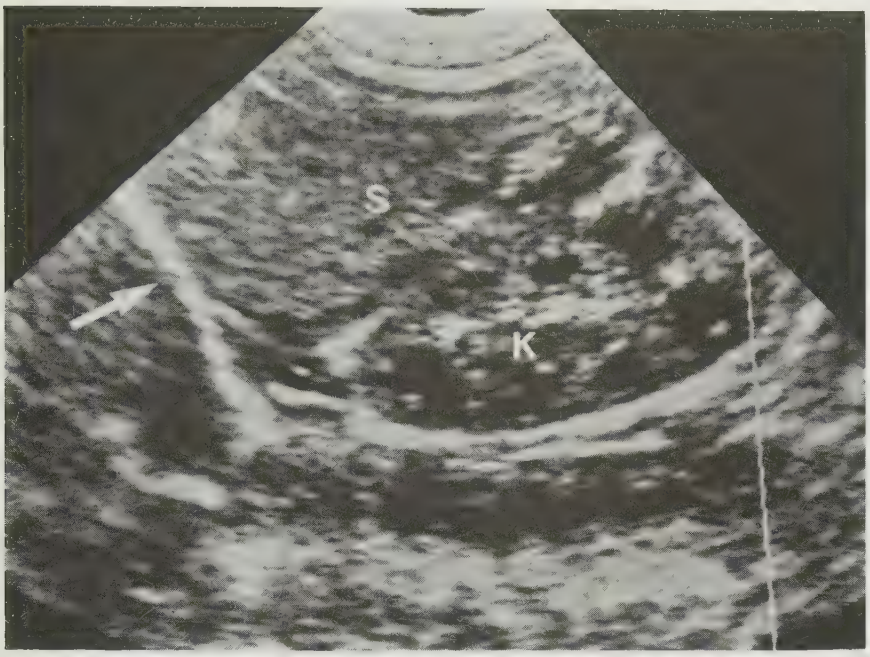


Fig. 75–14. Abdominal ultrasonogram in a neonate with cyanosis, situs inversus of abdominal viscera, and levocardia. This right parasagittal scan demonstrates splenic tissue between the right kidney (K) and the right hemidiaphragm (arrow). Patient's head is toward the left, feet toward the right of illustration. (Courtesy of Dr. Joan McIlhenny.)

Exceptions

Although the concept of asplenia and polysplenia as distinct syndromes has some clinical utility, it is important to realize that many "crossover" cases exist and there is nothing to suggest a causal relationship between the absence of the spleen (or the presence of several) and congenital heart disease. The heart may be completely normal in the presence of asplenia.[155,182–185] Conversely, many of the features of the "asplenia syndrome" have been reported in the presence of a normal or rudimentary spleen.[186,187]

Certain cardiovascular abnormalities occur with such a high frequency that they are often considered pathognomonic for asplenia or polysplenia. The presence of the inferior vena cava and abdominal aorta on the same side of the spine has been considered specific for asplenia,[146] but the patient with this finding depicted in Figure 75–11 clearly has splenic tissue. Similar examples have been described by others.[180,188] Likewise, although azygous continuation of the inferior vena cava is strongly suggestive of polysplenia, the patient depicted in Figure 75–9 had asplenia at autopsy. An attempt by Landing and colleagues[189–191] to explain exceptional cases by creation of additional syndromes (m-, f-, and o-anisosplenia) has not been adopted widely.

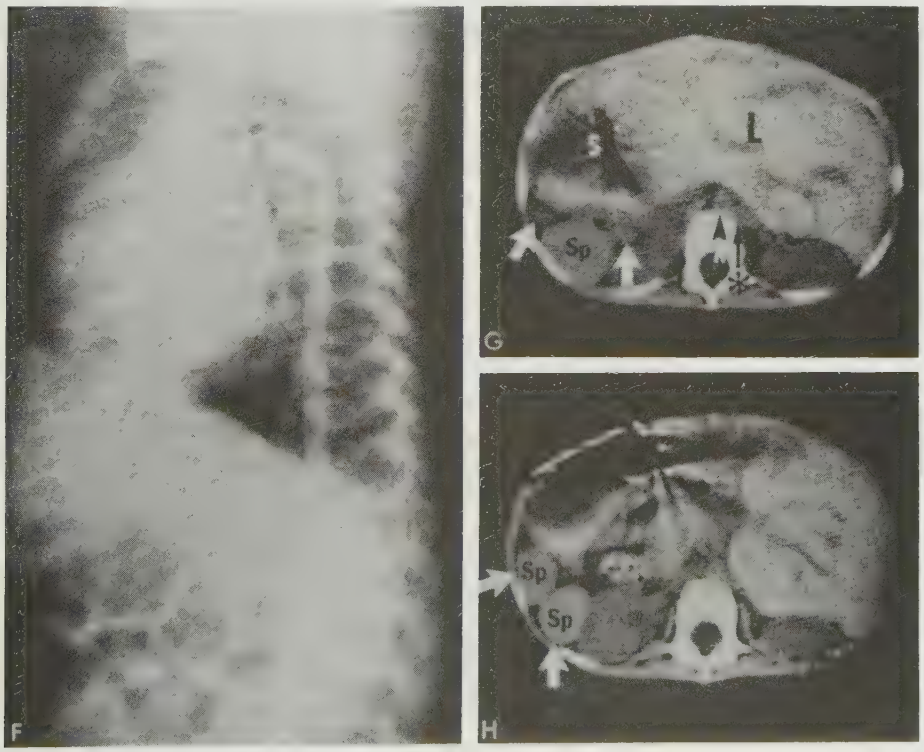


Fig. 75–15. Angiocardiogram and computed tomographic (CT) scan in polysplenia. The lateral projection of the angiocardiogram (F) demonstrates the frequent finding of azygous continuation of the inferior vena cava. The CT scan (G and H) shows a left-sided liver (L) and abdominal aorta (A) and a right-sided stomach (S). Several masses of splenic tissue are apparent (Sp, arrows). The asterisk indicates the location of the azygous vein on the CT scan (G). (From Tonkin, I.L.D., The definition of cardiac malpositions with echocardiography and computed tomography. *In* Pediatric Cardiac Imaging. Edited by W.F. Friedman and C.B. Higgins. Philadelphia, W.B. Saunders, 1984, pp. 157–187. Reproduced with permission.)

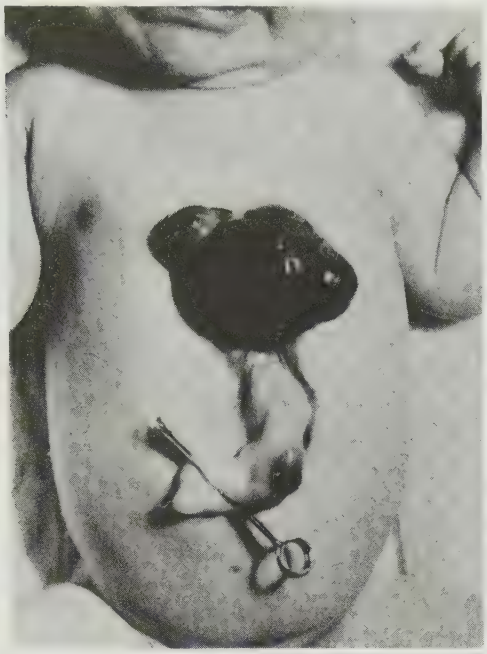
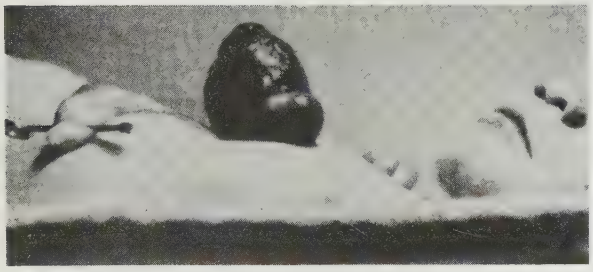


Fig. 75–16. Frontal (upper) and lateral (lower) views of newborn infant with thoracic ectopia cordis. Patient died after attempt to place heart in left pleural space. Intracardiac anatomy was normal except for a left superior vena cava and patent ductus arteriosus. (From Milhouse, R.F., and Joos, H.A.: Extrathoracic ectopia cordis: Report of cases and review of literature. Am. Heart J., *57*:470, 1959. Reproduced with permission.)



Although the asplenia syndrome has features of bilateral right-sidedness, and polysplenia simulates bilateral left-sidedness, numerous exceptions to this rule occur. Only 60 to 70% of patients with polysplenia actually have two morphologic left lungs (see Table 75–4). Additionally, the bronchi and atria may be discordant[192] and *left* atrial isomerism has been described in a patient with asplenia.[193]

ECTOPIA CORDIS

Historical Aspects

Ectopis cordis is the rarest and certainly the most dramatic of the cardiac malpositions. Byron[194] found only 142 cases reported prior to 1948. The earliest report is by Niels Stensen, whose 1671 description of the internal anatomy of the ectopic heart also appears to be the first account of the anomaly now known as the tetralogy of Fallot.[195] Greig's[196] review covers virtually all cases published before 1926. He credits Todd (1836) and Townsend (1845) with classification of ectopia cordis into three types: 1) cervical; 2) thoracic; and 3) abdominal. More recently, a fourth type, thoraco–abdominal, has been described.[194] Many of the earlier reports of abdominal ectopia cordis were probably of the thoraco–abdominal type, with true abdominal ectopia cordis being extremely rare.

Embryology

All forms of ectopia cordis appear to represent incomplete fusion of the converging lateral body walls in the midline. The defect may be established as early as the third week of gestation when the demarcation between intra- and extraembryonic coelom is established.[199] Simple failure of the sternal precursors to fuse completely in the midline results in mild or partial forms of ectopia cordis in which the sternal defect is covered with skin and the heart is palpable (or even visible), but not actually protruding from the thorax.

The complete forms of ectopia cordis may occur as a result of the heart being "trapped" outside of the thorax as the lateral body walls converge in the midline.[199] The thoraco–abdominal forms of ectopia cordis appear to represent failure of fusion of the lower sternum and defective development of the septum transversum, which forms the anterior portion of the diaphragm.[199–201]

Intracardiac Anatomy

Intracardiac abnormalities are very common, but not invariable, in patients with ectopia cordis. Atrial septal defect, ventricular septal defect, tetralogy of Fallot, and tricuspid atresia are the most common intracardiac defects.[194–197,200–205] An additional malfor-

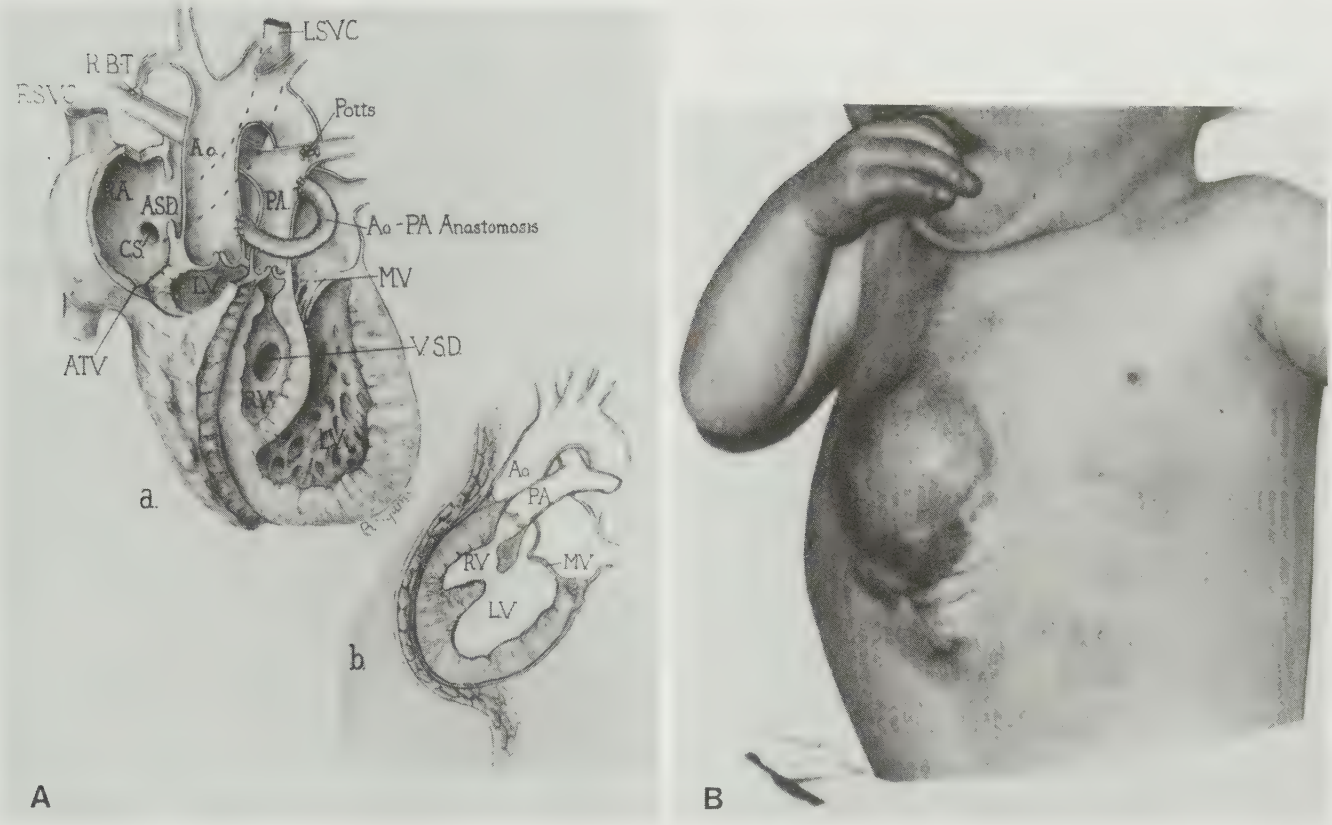


Fig. 75–17. Thoraco-abdominal ectopia cordis with tricuspid atresia. On the first day of life, an operation was performed and a large omphalocoel was covered with skin. Cardiac catheterization revealed tricuspid atresia with pulmonary stenosis (A), which was treated with a series of systemic-pulmonary artery anastomoses. At 13 months of age (B), the residual midline defect was apparent: Most of the left and right ventricles were still outside of the thorax. Patient also had the mosaic form of Turner's syndrome. Ao = aorta; ASD = atrial septal defect, ATV, atretic tricuspid valve, CS = coronary sinus, LSVC = left superior vena cava, LV = left ventricle, MV = mitral valve, PA = pulmonary artery, RA = right atrium, RBT = right Blalock–Taussig anastomosis, RSVC = right superior vena cava, RV = right ventricle, VSD = ventricular septal defect. (From Garson et al. Thoracoabdominal ectopia cordis with mosaic Turner's syndrome: Report of a case. Pediatrics, *62*:218, 1978. Reproduced by permission of Pediatrics.)

mation, a diverticulum protruding from the apex of the left ventricle, is present in 20% of the patients with the thoraco–abdominal defect,[206–209] and is virtually never present in other subjects, with or without ectopia cordis.

Treatment and Prognosis

The treatment and prognosis in ectopia cordis are largely determined by three variables: 1) the location of the defect; 2) the extent of the cardiac displacement; and 3) the intracardiac anatomy. Simple sternal clefts with absent or minimal cardiac protrusion can be repaired in early infancy with direct opposition of the edges of the defect or use of a prosthetic mesh.[201,210] At the other extreme, complete protrusion of the heart through a sternal defect—ectopia cordis extrathoracica nuda—is almost invariably fatal (Fig. 75–16). Ravitch[201] found descriptions of 20 operated patients with only 2 survivors; Van Praagh[21] described a third survivor.

The thoraco–abdominal form of ectopia cordis (Fig. 75–17) lies between these extremes. Typically, the lesion exists as part of a constellation of associated anomalies, which several investigators believe should be distinguished from ectopia cordis.[200,201,205,208] The lesions include: 1) midline supra-umbilical abdominal defect; 2) defect of the distal sternum; 3) deficiency of the diaphragmatic pericardium; 4) deficiency of the anterior diaphragm; and 5) congenital intracardiac abnormality, a constellation of anomalies sometimes referred to as the pentalogy of Cantrell.[200] The presence of an omphalocoel, as opposed to simple umbilical hernia, is an important risk factor and requires immediate surgical therapy.[211,213]

Patients without omphalocoel or intracardiac defects may remain largely asymptomatic and can undergo surgical repair later in childhood.[214] The major difficulty in repair of this and other forms of ectopia cordis is cardiorespiratory insufficiency following attempts to force the heart into the thorax.[215]

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CHAPTER 76

Clinical Physiology of Obstructive and Regurgitant Lesions

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Valvular abnormalities account for most obstructive and regurgitant lesions in childhood. The remainder of cases are characterized by obstructions proximal or distal to the valves. The clinical importance of an obstructive or regurgitant lesion is determined by the anatomic site of obstruction, the severity of the obstruction, or amount of regurgitation, the presence of other cardiac abnormalities (such as other obstructive or regurgitant lesions or shunts), the age of the patient, and the status of the patient's myocardial function.

ANATOMIC LOCATION OF THE LESION

The anatomic location of an obstruction influences the clinical manifestations in a number of ways. An obstructive lesion in the systemic venous system causes venous plethora and edema in the segment drained by the obstructed venous segment. Consider as an example a case of superior vena caval obstruction syndrome from a thrombus in the superior vena cava. Obstruction within the right atrium (e.g., from a right atrial myxoma or thrombus) and tricuspid valve stenosis also may cause systemic venous congestion and peripheral edema. Right ventricular outflow obstruction may be due to valve obstruction or may result from abnormal muscle in the right ventricle below the pulmonary valve. Differences in natural history, physiology, and management exist based on different anatomic locations of the right ventricular outflow obstruction. Pulmonary valve stenosis is easier to treat (i.e., with balloon valvuloplasty) than is subvalvular right ventricular outflow tract obstruction (which requires myomectomy). Subpulmonic, infundibular obstruction often becomes progressively severe. Although the severity of valve pulmonary stenosis also may progress in some cases, it is comparatively uncommon for valve pulmonary stenosis to worsen over the years. Obstructions may occur above the pulmonary valve as well. Supravalvular stenosis is generally diffuse and may extend to the branch pulmonary arteries. A single, narrow, discrete obstruction of the pulmonary trunk is uncommon (except for the case of a surgically placed pulmonary artery band) in contrast to the typically localized nature of aortic coarctation. Distal pulmonary artery stenosis may complicate or preclude surgical therapy.

There are several anatomic locations of lesions that cause obstruction of return of the pulmonary venous blood to the left ventricle as discussed in Chapter 77; Cor Triatriatum, Pulmonary Vein Obstruction, Supravalve Mitral Stenosis, and Congenital Mitral Valve Disease. Included are cases of pulmonary vein stenosis, pulmonary vein atresia, anomalous pulmonary venous return with obstruction (either intracardiac or extracardiac), baffle obstruction from a Mustard or Senning operation, cor triatriatum, supravalvar mitral membrane, and mitral stenosis. Pulmonary venous hyper-

Table 76–1. Factors Determining the Clinical Significance of an Obstructive or Regurgitant Lesion

Anatomic locations of the lesion
Magnitude of the lesion (severity of obstruction or amount of regurgitation)
Presence of other hemodynamic burdens (other obstruction or regurgitation or shunt)
Age of the patient
Impairment of myocardial contractility

tension causes stiff lungs which increase the work of breathing. Symptomatic pulmonary edema with tachypnea and wheezes are common in these lesions, which are sometimes confused with lung disease. Pulmonary arterial hypertension develops as does pulmonary arteriolar hypertension, resulting in physical findings of pulmonary hypertension and right ventricular pressure overload.

Left ventricular outflow obstruction may be at the subvalve, valve, supravalve, or aortic level. Common to these obstructions is an increased afterload for the left ventricle. Ventricular hypertrophy, ventricular dilation, and impaired ventricular function will result, depending upon the chronicity and severity of obstruction. Subaortic obstruction may be associated with aortic regurgitation and thus has clinical significance beyond the severity of left ventricular outflow tract obstruction per se. An obstruction proximal to the coronary artery ostia (such as subvalvular or valvular aortic stenosis) is more likely to be associated with a myocardial blood flow demand/supply mismatch and myocardial ischemia than is a left ventricular outflow obstruction beyond the coronary ostia (such as supravalvar aortic stenosis or coarctation of the aorta).

This has been suggested to be of clinical importance for the infant with both severe coarctation of the aorta and severe aortic stenosis as one proposes a strategy for a surgical intervention upon one or both lesions. Poststenotic dilation of the ascending aorta can reach aneurysmal proportions in aortic valve stenosis and require surgery on the aorta in adult years in rare instances. The anatomic location of coarctation of the aorta will affect the management strategy in some coarctation cases as discussed in Chapter 80, Coarctation of the Aorta and Interrupted Aortic Arch, and Chapter 131, Surgical Decision Making. The site of coarctation obstruction in relation to the ductus arteriosus is of clinical importance prior to closure of the ductus or if one attempts to use prostaglandin E1 for stabilization of an infant with a severe coarctation of the aorta. The anatomic site of coarctation relative to the subclavian arteries will be of importance if one plans to use the subclavian artery in the repair. Hypoplasia of the aortic isthmus may be present with infant coarctations (''coarctation syndrome''), as discussed in Chapter 80, Coarctation of the Aorta and Interrupted Aortic Arch, and may be an important source of residual obstruction after a technically adequate repair of coarctation of the aorta in the newborn.

The location of a regurgitant lesion also influences the clinical manifestations. Tricuspid regurgitation of mild and moderate severity is tolerated very well. Severe tricuspid regurgitation (particularly if associated with right ventricular hypertension) causes systemic venous congestion. Chronic right atrial enlargement from tricuspid regurgitation may lead to atrial flutter or fibrillation. Isolated pulmonary regurgitation generally is tolerated quite well. Although there may be deleterious consequences of long-standing right ventricular volume overload and extremely long followup is unavailable, in most cases, even severe pulmonary regurgitation seems to be tolerated surprisingly well after pulmonary valvectomy for pulmonary valve stenosis or after transannular patch for tetralogy of Fallot. If it is severe, mitral regurgitation causes left atrial hypertension with symptoms of pulmonary edema. Severe mitral regurgitation will cause left atrial dilation and may result in atrial arrhythmias. The high velocity left ventricular to left atrial jet occasionally is associated with intravascular hemolysis—particularly if prosthetic patches or valves have been implanted. Mitral regurgitation is a lesion that results in an afterload reduction for the left ventricular myocardium. Surgical correction of severe mitral regurgitation can increase the afterload of the left ventricle and—in the presence of impaired left ventricular myocardial function before surgery—result in a severely compromised patient in the postoperative unit. Severe aortic regurgitation, in contrast, is a volume load on the left ventricle. Surgical treatment of the case with severe aortic regurgitation and myocardial failure is tolerated better, from the aspect of ventricular function, than surgical treatment of the case of severe mitral regurgitation with myocardial failure.

MAGNITUDE OF THE LESION

It is intuitive that the more severe a given lesion, the more likely it is to be clinically important. How one assesses the severity of an obstruction is less intuitively obvious. Clinical features may give clues to the severity of an obstruction. With increasing severity of semilunar valve stenosis, the murmur generally becomes louder and peaks later in systole. The most severe obstructions will be associated with a very soft murmur because of low cardiac output due to the critical valve obstruction and/or ventricular dysfunction. The severity of a valvular lesion is assessed clinically by the consequences proximal to the obstruction. For example, ascites hints at the severity of tricuspid stenosis and wheezing or tachypnea from pulmonary venous hypertension reflects the severity of mitral stenosis. In aortic or pulmonary stenosis, ventricular hypertrophy with decreased compliance may be responsible for reduced filling and reduced cardiac output. The low cardiac output from critical obstruction may obscure the diagnosis or cause confusion in assessment of severity. Assessment of the severity of tricuspid and mitral obstruction from proximal effects is adequate for most purposes. Assessment of the significance of pulmonary stenosis by the character of the murmur and the degree of the right ventricular hypertrophy by electrocardiography usually is sufficient for purposes of following the patient. The severity of aortic stenosis is difficult to determine precisely by history, physical examination, or electrocardiographic criteria. The clinician depends more on echocardiography and catheterization in the assessment of the clinical physiology of aortic stenosis than for pulmonary stenosis.

The severity of obstruction is assessed commonly in the catheterization laboratory by measurement of the transvalvar pressure gradient. Most longitudinal natural history data and recommendations for therapeutic interventions are based on the transvalvar pressure gradients. These gradients are output-dependent. Under sedation, a high cardiac output state could exist that would cause an overestimate of severity; ventricular failure with a low cardiac output would cause an underestimate of the severity of obstruction by use of the transvalvar pressure gradient. Another potential problem with the use of the peak systolic ventricular to peak systolic arterial pressure difference is that—particularly with aortic valve stenosis—noninvasive gradient calculation from the Doppler formula (which measures an instantaneous gradient) will give a higher number. This is so because the peak instantaneous pressure gradient actually is higher than the peak-to-peak pressure gradient (see Chapter 47, Doppler Echocardiography). This difference leads to confusion when those inexperienced with Doppler measurements make clinical decisions based on these measurements. Grading of the severity of semilunar stenosis by hemodynamic measures also can be based upon calculation of the valve area as

discussed in Chapter 54, Cardiac Catheterization—Hemodynamic Measurements. Calculation of valve area is cumbersome and, in most pediatric cardiac catheterization laboratories, is infrequently performed. Cardiac output always should be measured when one is judging the severity of an obstructive lesion. If there is a question of interpretation of the transvalvar pressure gradient because of a low or high cardiac output, it is helpful to have a calculation of the valve area.

The severity of regurgitant lesions may be assessed clinically. Tricuspid and mitral valve regurgitation result in a large systolic flow from ventricle to atrium followed by an increased amount of forward flow across the regurgitant atrioventricular valve during diastole. The low-frequency mid-diastolic murmur that results is often referred to as a Carey Coombs murmur (see Table 10–43). If a diastolic flow rumble is not present, the atrioventricular valvular regurgitation is of mild severity. Assessment of the severity of atrioventricular valve regurgitation by cardiac catheterization can be useful. The height of the "v" (or, more correctly, "r" for "regurgitant") wave of the atrial pressure tracing depends on the ventricular contractility as well as the severity of regurgitation. The atrial mean pressure is elevated when severe atrioventricular valve regurgitation is present. Angiography can contribute to the assessment of the severity of atrioventricular valve regurgitation. With severe atrioventricular valve regurgitation, the atrium is dilated and pulsations synchronous with ventricular systole may be seen in the hepatic veins in tricuspid regurgitation or the pulmonary veins in mitral regurgitation.

Mild degrees of regurgitation may be caused by a catheter traversing the atrioventricular valve. Thus, the retrograde approach generally is preferred for quantifying mitral regurgitation. An injection without premature ventricular contractions is important because catheter-induced premature beats cause regurgitation during angiography. Echocardiography contributes to the assessment of severity of atrioventricular valve regurgitation. With severe regurgitation, the atrium is dilated and a regurgitant jet can be mapped by Doppler to the venous attachments of the atrium. A broad regurgitant jet can be identified by color Doppler or by a careful, pulsed Doppler mapping. The velocity of the regurgitant jet will be related to the pressure difference between the atrium and ventricle in systole. Therefore, very mild mitral regurgitation can be expected to have a high velocity; a high velocity does not relate to the severity of the regurgitation.

The more severe the aortic or pulmonary valve regurgitation, the longer the murmur will be. Usually, the semilunar valve regurgitation murmur does not become louder with more severe regurgitation, it just becomes longer. The clinical assessment of the severity of pulmonary valve regurgitation is based on evidence of volume overload of the right ventricle. Aortic regurgitation may be associated with a low-frequency diastolic murmur at the apex from the regurgitant jet of blood, causing vibration of the anterior leaflet of the mitral valve (the Austin Flint murmur). If there is no Austin Flint murmur, the aortic regurgitation is generally mild. Peripheral manifestations of diastolic runoff (such as Corrigan pulses and Quinke's capillary pulse, as discussed in Chapter 43, History and Physical Examination) identify aortic regurgitation as severe.

Echocardiographic criteria for severe aortic regurgitation are, for the most part, based on the amount of diastolic runoff (such as reversal of flow in the aorta and prominant pulsatility of the aorta) and do not offer a great deal more precision in assessment than what is available from a careful physical examination. The important echocardiographic questions in the assessment of the physiology of aortic regurgitation for the clinician are "How dilated is the left ventricle?" and "How well does the left ventricle contract?" Angiographic assessment of the severity of aortic regurgitation relies on how many cardiac cycles are required to clear dye from the left ventricle. Aortic regurgitant lesions of mild severity will clear dye from the left ventricle after aortic root injection within several heart beats. Increasingly severe regurgitation will take longer and longer to clear dye. There are several methods to calculate the regurgitant fraction (see Chapter 54, Cardiac Catheterization—Hemodynamic Measurements). The regurgitant volume can be calculated by taking the difference between the left ventricular angiographic output (ventricular volume calculated by planimetry of systolic and diastolic frames using Simpson's rule or the area-length method times the heart rate) and the pulmonary blood flow (from thermodilution method). However, the most important aspects in the surgical decisions on aortic regurgitation in childhood involve the progressive increase in left ventricular size and decrease in left ventricular contractility—and not the regurgitant fraction.

PRESENCE OF OTHER HEMODYNAMIC BURDENS

Shone's syndrome of multiple left heart obstruction includes obstruction in LV inflow, LV outflow, and aorta. Associated defects may either increase or decrease the apparent severity of regurgitant or obstructive lesions. The obstruction to pulmonary venous return in a case with anomalous pulmonary connection and pulmonary atresia (a frequent combination in right atrial isomerism, "asplenia") may not be apparent until after an aorticopulmonary shunt is performed to increase pulmonary blood flow. Lutembacher's syndrome is an atrial septal defect with mitral stenosis. The presence of an atrial septal defect minimizes the likelihood of left atrial hypertension developing and makes the obstruction at the mitral valve subtle clinically. Multiple levels of obstruction also can alter the clinical physiology of an obstructive lesion. For example, if there is tetralogy of Fallot with severe obstruction at the level of the pulmonary valve, a severe distal obstruction at the level of the branching of pulmonary arteries would be less apparent than would be the case after the defect is repaired and the pulmonary obstruction is relieved because of the low pulmonary blood flow preoperatively. The same phenomenon can occur with multiple sites of obstruction on the left side of the heart. Pulmonary valve stenosis with an intact ventricular septum, in contrast, can minimize a potential infundibular obstruction with the severe right ventricular hypertension "stenting" open a hypertrophic infundibulum. This phenomenon can create a severe, although usually transient, subpulmonic outflow tract obstruction after surgical or catheter treatment. The clinical physiology of a regurgitant lesion also is potentially greatly influenced by the presence of other lesions. Tricuspid regurgitation could be critical if there was right ventricular volume overload from pulmonary regurgitation or right ventricular pressure overload from pulmonary stenosis. The presence of an obstruction at the same site as the regurgitation also can affect the clinical physiology of a regurgitant lesion. Aortic stenosis and aortic regurgitation often occur together. The combined pressure and volume overload cause a greater hemodynamic

burden for the left ventricle and a greater myocardial blood flow demand/supply mismatch than is found with either lesion alone.

AGE OF THE PATIENT

The age of the patient is an important factor in the clinical physiology of obstructive lesions. Severe left-sided obstructive lesions in the newborn generally are associated with a dilated left ventricle without hypertrophy. The same severity of obstruction developing gradually in the older child results in left ventricular hypertrophy, usually with a normal-sized left ventricular cavity. The abrupt transition from a predominantly right ventricular systemic pump (fetal circulation) to the neonatal (predominantly left ventricular) systemic pump in the case of a left-sided obstruction is very different physiologically from the same obstruction developing later in life. The neonate's myocardium has functional differences from the myocardium of the adult or older child. This age-related functional difference may result in less reserve for the neonate to adapt to the abnormal hemodynamics caused by an obstructive or regurgitant lesion.

IMPAIRMENT OF MYOCARDIAL CONTRACTILITY

Acute development of severe obstruction or regurgitation is more likely to result in rapid deterioration of hemodynamic function and myocardial function than obstruction or regurgitation that develops gradually. With chronic obstruction or regurgitation, adaptations of the myocardium to normalize wall stress occur. Hypertrophy has the disadvantage of resulting in an increased amount of muscle that requires delivery of blood from the coronary circulation. An increase in the metabolic demand of the myocardium can accompany this. If there is severe diastolic ventricular pressure overload, myocardial blood flow (particularly to the subendocardial regions) can be deleteriously affected by a high intramyocardial pressure. Extremes of chronic pressure overload and chronic volume overload will lead to myocardial fibrosis and ventricular dysfunction. Myocardial ischemia is probably a major contributor to this process. Development of ventricular dysfunction will clearly change the functional importance and clinical findings of an obstructive or regurgitant lesion.

CHAPTER 77

Cor Triatriatum, Pulmonary Vein Obstruction, Supravalvar Mitral Stenosis, and Congenital Mitral Valve Disease

Janette F Strasburger

COR TRIATRIATUM

Cor triatriatum is thought to result from embryologic failure of the common pulmonary vein to become incorporated into the left atrium during the fifth week of embryonic development.[1] This results in a fibromuscular membrane that subdivides the left atrium into a venous portion, sometimes called the proximal chamber (since it is proximal to the site of obstruction), and a true left atrial portion, referred to as the distal chamber. In almost all cases the left atrial appendage is distal to the cor triatriatum membrane. The location of the fossa ovalis is variable, and atrial septal defects may be present in either the proximal or distal chamber.[2,3] In the typical form of cor triatriatum, the "windsock" funnel-shaped membrane is perforated by a single hole (90%) or less commonly, multiple fenestrations (10%). Cor triatriatum can occur with associated partial anomalous pulmonary venous connections, or it can involve only two pulmonary veins. Sometimes in this situation there are also atrial septal defects. Cor triatriatum is differentiated from supravalvar mitral ring by the fact that the membrane in supravalvar mitral ring is usually shelf-like and located just superior to the mitral annulus. Supravalvar mitral ring rarely occurs as an isolated defect.

Cor triatriatum is a rare congenital anomaly, occurring in 4% of patients with cardiac defects.[4] In one autopsy series, it occurred as an isolated defect in 7 of 20 patients, and in the remainder, was associated with other congenital anomalies.[2] The most common associated anomaly was patent ductus arteriosus in 17%, anomalous pulmonary venous connections 8.6%, left superior vena cava 8%, and ventricular septal defect 7%.[2,5] Cor triatriatum has also been reported in combination with coarctation of the aorta, sinus venosus atrial septal defect, tricuspid atresia, Shone's syndrome, atrioventricular canal defect, tetralogy of Fallot, congenital mitral regurgitation, and Ebstein's malformation.[1–8] The male/female ratio is 1.4:1.[2] Familial recurrences have not been cited. Often cor triatriatum occurs in association with defects that may obscure its recognition. A large membrane opening in the left atrium, decompression of the proximal chamber due to an atrial septal defect, and decreased pulmonary blood flow may all contribute to a delay in the diagnosis of cor triatriatum.[1]

Cor triatriatum usually presents during infancy with symptoms of failure to gain weight; diaphoresis, and recurrent respiratory infections. Its presentation is similar to that of mitral stenosis. Eighty-five percent of patients with cor triatriatum presented under 40 yr of age and 8 of 20 presented under 1 yr of age. Rarely, however, individuals have presented during adulthood with chest fullness, dyspnea on exertion, cough, hemoptysis, atrial fibrillation, or other signs of pulmonary venous hypertension.[7] The age at clinical presentation usually depends on the degree of obstruction to left atrial blood flow, and in the presence of associated left-to-right shunts or other cardiac defects.[1–3,7]

The chest roentgenogram in cor triatriatum usually shows redistribution of blood flow with increased pulmonary vascular markings suggestive of pulmonary venous congestion.[1,7] The heart size is normal or only mildly enlarged. The left atrial shadow is usually not prominent in radiographs of children. The electrocardiogram may be normal; however, right-axis deviation, right atrial or biatrial enlargement, and right ventricular hypertrophy are more commonly seen. Atrial fibrillation is less common in patients with cor triatriatum than with mitral stenosis, and this arrhythmia rarely occurs in children.

On physical examination, the precordium is quiet unless pul-

monary arterial pressure is elevated, when there may be a right ventricular lift. S1 is usually normal, without an opening snap. The pulmonary component to the second heart sound may be increased. A soft, grade I-II/VI diastolic or continuous murmur is often audible at the left upper sternal border. Although infants generally present with dyspnea, failure to thrive, and pulmonary infections, older patients sometimes present with syncope, hemoptysis, or right heart failure. In patients with left-to-right shunts due to partial anomalous venous connections or proximal atrial septal defects, the symptoms and findings on physical examination may be those of a large left-to-right shunt. The electrocardiographic and radiographic features in these patients are similar to those of other patients with cor triatriatum; however, on physical examination, the second heart sound is usually widely split.[1,2,7]

Two-dimensional echocardiography from the left parasternal long-axis and apical or subcostal views, demonstrates a nonmobile membrane traversing the left atrium.[9–11] It is usually adherent to the upper portion of the left atrial lateral wall, and may at times be attached to the atrial septum. The mitral valve is not attached to the membrane but may show diastolic fluttering because of diastolic turbulent left atrial flow. Care must be taken to trace the entrance of all four pulmonary veins, especially if surgery is to be carried out without catheterization. Location of the patent foramen ovale and atrial septal defects is possible using a combination of two-dimensional echocardiography and pulsed Doppler.[12] Transesophageal echocardiography has been useful in proving the diagnosis in adult patients with poor anterior thoracic windows; however, the technique requires introduction of a gastroscopic transducer and is rarely necessary in pediatric patients.[1,4,7,9,10]

Three types of cor triatriatum have been described: 1) a fibromuscular diaphragm with no external deformity, 2) an hourglass constriction of the left atrium, and 3) an elongated tubular accessory left atrial connection. The diaphragm is composed of thickened endocardial tissue and muscle fibers, and is the most common form. Neither of the other forms contains this diaphragm. Examination of the lungs generally reveals only mild pulmonary vascular changes consistent with pulmonary arterial and venous vasoconstriction. These changes include medial hypertrophy and extension of muscularity into small arteries.[2]

At catheterization, elevation in pulmonary artery pressure is usually present. Misleadingly normal capillary pulmonary wedge pressures have been reported,[1,11] although generally, the pulmonary capillary wedge pressure is elevated.[2] The levophase of a pulmonary artery injection in the cranially angulated anteroposterior projection usually demonstrates associated anomalous pulmonary venous connections and atrial septal defects when present. Entry of the distal chamber by the transseptal approach, or via a patent foramen ovale can allow careful probing for the presence of a gradient across the orifice of the left atrial membrane. If the orifice of the proximal chamber is small, acute compromise in cardiac output can occur. Injection in the distal chamber in the left atrium demonstrates the subdivided left atrium and the left atrial appendage. A left ventricular injection can be performed to rule out mitral valve anomalies and other associated cardiac defects. When multiple cardiac defects are present, the diagnosis of cor triatriatum must be suspected, since it is often missed at catheterization in this situation.[1,2,4,7]

Surgical management is the treatment of choice for cor triatriatum and usually involves excision of the intra-atrial membrane. Dilation of the membrane intraoperatively has been associated with recurrence of stenosis. Reported mortality for all ages of patients is approximately 16%, but may be as high 25 to 50% in the sick neonate with associated major cardiac defects. No significant late mortality has been reported from arrhythmias or other problems. Reversal of pulmonary hypertension usually occurs unless there is residual obstruction or other defects. Often the membrane can be excised through the atrial septum, although the operation does require cardiopulmonary bypass.[13,14]

SUPRAVALVAR STENOSING MITRAL RING

Supravalvar mitral ring, or supravalvar stenosing ring of the left atrium, is an uncommon congenital anomaly consisting of a shelf-like fibrous ridge, or connective tissue invagination of the left atrial wall overlying the mitral orifice and often attached to the mitral annulus circumferentially.[7] Although its embryologic development is not clearly understood, it may result from abnormal atrial septation or defective subdivision of the endocardial cushions during early development of the heart.[15] In 90% of cases, supravalvar mitral ring is associated with other cardiac defects, most commonly with the Shone's anomalad of subaortic stenosis, parachute mitral valve, coarctation of the aorta and sometimes ventricular septal defect. Other anomalies associated with supravalvar mitral ring include ventricular septal defect alone, mitral valve stenosis and shortened chordae tendineae, patent ductus arteriosus, double-outlet right ventricle, and complete atrioventricular canal defect. The clinical presentation of supravalvar mitral ring is similar to that of other left-sided cardiac obstructive lesions described in this chapter. Most patients are symptomatic before 2 yr of age.

A number of patients have had successful surgical management of this defect. The operation usually consists of dissection of tissue away from the annulus and the mitral valve and excision of the ridge. One report has described a nonconcentric supravalvar mitral ridge containing the left circumflex coronary artery, so that care must be taken to avoid injury of the coronary arterial system.[16] Preoperative evaluation of coronary artery distribution is probably indicated. The prognosis of supravalvar mitral ridge is generally dependent on the severity of associated cardiac anomalies.[15]

UNILATERAL PULMONARY VEIN STENOSIS OR ATRESIA

Unilateral pulmonary vein obstruction usually occurs as the result of complete or partial occlusion of the pulmonary vein orifice by a flap or valve of fibrous tissue. The obstruction may be discrete, or there may be diffuse pulmonary vein hypoplasia. Obstruction may involve one pulmonary vein. However, it is more common for two veins on one side to be involved. This defect is extremely rare, occurring in about 1 in 30,000 children evaluated for congenital heart disease.[17,18] Approximately 50% of cases are associated with congenital intracardiac defects.[19,20] Associated lesions include ventricular septal defect, transposition of the great arteries, and less commonly, mitral atresia, systemic or pulmonary artery anomalies, coarctation of the aorta, patent ductus arteriosus, atrial septal defect, tetralogy of Fallot, and tricuspid atresia. Pulmonary vein obstruction may also be present in total or partial anomalous pulmonary venous connection, either congenitally or secondary to

surgical repair. Unilateral pulmonary vein obstruction appears to have an equal incidence of right and left pulmonary vein obstruction. However, with particular cardiovascular lesions, involvement of one side is predominant. For example, with ventricular septal defect, 75% of patients have had right-sided obstruction, whereas with transposition of the great arteries, all have had congenital left-sided obstruction. It has been postulated that the side of obstruction is related to preferential flow to the contralateral lung in these particular cardiac defects. In Driscoll and colleagues' review of 38 cases, seven involved stenosis of all four veins.[21] No sex predilection has been noted.[17,20–23]

Most cases of pulmonary vein obstruction are felt to be congenital because 1) there is a high incidence of associated congenital heart defects, 2) symptoms frequently develop early in life, 3) histology fails to suggest inflammation of the pulmonary vein orifices, 4) hypoplasia of the ipsilateral lung is also often present, and 5) similar types of obstruction occur with known forms of congenital heart disease such as anomalous pulmonary venous drainage. A number of acquired conditions can result in pulmonary vein obstruction as well, and these include obstruction due to atrial baffle procedures, pulmonary veno-occlusive disease, mediastinal tumor, mediastinitis, constrictive pericarditis, and extension of a left atrial myxoma or thrombus. In one case, unilateral pulmonary vein obstruction has been associated wth maternal Hashimoto's thyroiditis.[17,24]

The exact embryologic cause of pulmonary vein stenosis is not known. It is likely that this defect occurs relatively late in the formation of the heart, possibly after the common pulmonary vein is fully incorporated into the left atrium. In situations in which diffuse hypoplasia of the pulmonary vein has occurred, pulmonary flow was probably interrupted earlier, during the developmental period of pulmonary vein growth. It is also possible that destructive processes occurring within the left atrium during cardiac development could result in scarring of the pulmonary vein orifices.[19,23,25,26]

Unilateral pulmonary vein obstruction is generally well tolerated by the fetus, since bronchocollateral circulation vents the obstructed lung vessels. Bronchial-to-pulmonary anastomoses occur at the capillary, postcapillary, and precapillary levels and are capable of carrying up to 10% of postnatal pulmonary blood flow. Decreased flow in utero and postnatally through the pulmonary circulation, however, often results in hypoplasia of the ipsilateral lung.[25,26]

The severity of symptoms and the age of presentation with unilateral pulmonary vein obstruction depend on the severity of stenosis or atresia, associated cardiac defects, the degree of contralateral pulmonary blood flow and pressure, and the degree of ventilation/perfusion mismatching and atelectasis. Complete absence of symptoms has been reported with this defect. However, recurrent pulmonary infections and failure to gain weight may occur during infancy or childhood. Hemoptysis has been reported in older children.[19,22,23,27]

Physical findings include unilateral decrease in breath sounds on the involved side secondary to atelectasis and infection, mild cyanosis and clubbing, and chronic productive cough. Results of cardiovascular examination may be normal, but in cases in which pulmonary artery pressure is elevated, the P2 component of the second heart sound is increased, and there may be a right ventricular lift. Although ipsilateral pulmonary hypoplasia is often present, this is typically too subtle to detect on physical examination.[23,27]

The chest roentgenogram is helpful and often shows unilateral pneumonia or atelectasis. Pulmonary vascular markings on the obstructed side are normal or decreased, whereas the uninvolved lung demonstrates pulmonary edema with Kerley B-lines and pleural effusions, secondary to increased pulmonary blood flow. There is often hyperinflation of the normal lung and hypoplasia of the involved lung. The heart size is usually normal, but the pulmonary artery may be prominent.[27,28]

Technetium-99m lung perfusion scans often show markedly decreased or absent flow to the involved lung.[29] Normally, the left lung receives 45% of pulmonary flow, whereas the larger right lung receives 55%. Limited experience with two-dimensional echocardiography imaging suggests that it is not very sensitive in detecting unilateral pulmonary vein obstruction, although with improving resolution, and color-flow Doppler capabilities, it may be possible in the future to detect abnormal flow velocities, narrowing, or turbulence at the pulmonary vein orifices.

At cardiac catheterization the pulmonary artery pressure can range from normal to systemic.[28] Saturations in the involved artery may be high because of collateral blood flow. Left atrial saturation is decreased because of ventilation perfusion mismatching. Cineangiography often demonstrates preferential flow to the uninvolved lung. Because of increased flow, the contralateral pulmonary veins may be distended, but transit time is normal. Contrast may reflux from the pulmonary artery in the involved side and wash to and fro in the small pulmonary artery branches. Pulmonary artery wedge angiography is usually helpful in demonstrating pulmonary vein atresia or severe stenosis.[16] The pulmonary vein may not be visualized or may have a long delay in transpulmonary transit. On pulmonary artery wedge angiography, collateral bronchial vessels may fill, which communicate with the azygous system. Hemodynamic findings generally include elevated pulmonary artery and pulmonary capillary wedge pressures. Although unilateral elevation of the wedge pressure would be expected, there is often bilateral elevation secondary to pulmonary artery vasoconstriction.[20,27]

Surgery is usually most successful when discrete stenosis of the pulmonary vein orifice is present. It is often difficult to determine preoperatively whether pulmonary vein hypoplasia also accompanies this stenosis or atresia. Obstruction has been relieved by resection and dilation or patch enlargement of the orifice (Heineke–Mikulitz procedure for pulmonary venoplasty). In situations in which pulmonary venous drainage cannot be reestablished, these lung sections should be removed to prevent reflex vasconstriction secondary to ventilation perfusion mismatching.[26,27,30,31]

Results of balloon dilation angioplasty for pulmonary vein stenosis have not been promising.[19,21] Late recurrence of stenosis has been reported with relatively sudden recurrence of cyanosis 4 wk after dilation. One case of septic shock accompanied the procedure, possibly related to manipulation of infected pulmonary tissue. Although the results of surgery have not been optimal, an attempt at reestablishing pulmonary venous drainage is usually warranted in the patient with symptoms or hemodynamic abnormalities.

Mortality for the operative procedure is higher at a young age. The mean age at successful operation has been 8.8 yr. Many children continue to have abnormal flow distribution patterns by

lung perfusion scans postoperatively even when symptoms have been eliminated, supporting the concept that diffuse pulmonary venous hypoplasia usually exists.[21,27]

COMMON PULMONARY VEIN ATRESIA

Obstruction of the common pulmonary vein occurs when there is failure of anastomosis of the pulmonary venous confluence with the left atrium, or conversely, where this union regresses or becomes atretic. Unlike partial or unilateral pulmonary vein obstruction, this defect results in a blind common pulmonary venous pouch posterior to the left atrium. In addition, there is no connection to systemic venous channels, as seen in anomalous pulmonary venous connection. Embryologically, this condition probably develops late after regression of the venous channels connecting the splanchnic venous system of the lungs to the systemic venous system. If regression of these connections has not occurred, then total anomalous pulmonary venous connection would develop with drainage via the cardinal or umbilico-vitelline connections.[32,33] Bronchial veins become the only course of egress of pulmonary blood flow through the lungs in utero. Despite this fact, there is little development of bronchocollateral circulation. The development of bronchocollaterals is generally stimulated by the presence of precapillary obstruction, low oxygen tension, and low pulmonary pressures.[25] These are all conditions not found in common pulmonary vein atresia.

Common pulmonary vein obstruction is an extremely rare cardiac defect, with fewer than 20 reported cases. There appears to be no sex or racial predilection or familial occurrence. The defect is also usually not associated with other major cardiac defects.[32,34]

The clinical presentation of common pulmonary vein obstruction occurs early and is similar to that of obstructed total anomalous pulmonary venous connection. Most infants present in the first minutes to hours of life with severe respiratory distress, cyanosis, and grunting, and do not improve despite ventilation and 100% oxygen. The natural history is death within 1 mo.[32,33] On cardiac examination they have a hyperdynamic precordium with a right ventricular lift. S1 and S2 are loud and single and usually no murmur is present. The chest radiograph is similar to that of obstructed total anomalous pulmonary venous connection, or pulmonary lymphangiectasia with severe pulmonary venous congestion and little or no cardiomegaly.

At cardiac catheterization, the pulmonary artery pressure is usually systemic or suprasystemic with an increased pulmonary capillary wedge pressure. There is systemic desaturation. On angiography, contrast fails to opacify the venous bed and left atrium. Obstructed total anomalous pulmonary venous connection must be excluded.[33]

The only treatment for common pulmonary vein obstruction is surgical reanastomosis of the common pulmonary vein to the left atrium. Even with expeditous surgical treatment, no long-term survival has been reported to date.[33] This may be related to prenatal pulmonary vascular changes.

On gross pathology, the lungs are firm, edematous, and congested. The lymphatics are large and dilated within engorged intralobar tissue. Pulmonary veins are thick-walled and both pulmonary arteries and pulmonary veins demonstrate medial muscular hypertrophy.[32,34]

CONGENITAL MITRAL VALVE ABNORMALITIES

A number of congenital abnormalities of the mitral valve affect neonates and children. These include congenital mitral stenosis, congenital mitral insufficiency, cleft mitral valve, hypoplasia of the mitral valve and mitral valve annulus, anomalous mitral arcade, double orifice mitral valve, and mitral prolapse.

Embryologic development of the mitral valve is attributable to several sources. The mital valve leaflets develop from the left endocardial cushion tissue, and the papillary muscles and chordae tendineae result from undermining of the underlying ventricular muscle. The annulus of the mitral valve is part of the fibrous skeleton of the heart. The mitral valve apparatus is composed of the mitral annulus, the anterior and posterior mitral valve leaflets, separated by their commissures, the chordae tendineae, and the anteromedial and posterolateral left ventricular papillary muscles.[35] The mitral valve always accompanies the left ventricle, so that in ventricular inversion, the right-sided atrioventricular valve is most like the mitral valve. The anterior leaflet of the mitral valve is shorter at the base than the posterior leaflet but has a longer base-to-apex length than the posterior leaflet. Its arterial supply is from the left coronary artery. The posterior leaflet is C-shaped and covers the posterior two thirds of the mitral annulus. It receives its arterial supply from branches of both coronary arteries. The annulus of the mitral valve is composed of fibromuscular tissue and therefore contracts during atrial systole and throughout ventricular systole, allowing the mitral valve leaflets to overlap in the coapted position. There is fibrous continuity between the anterior leaflet of the mitral valve and the noncoronary cusp of the aortic valve. The chordae tendineae are cord-like branching collagenous fibers that attach the underside of the mitral valve to the left ventricular papillary muscle. The papillary muscles themselves are positioned within the ventricle anterolaterally and posteromedially. Occasionally, the heads of the papillary muscles may be split. Being muscular, the purpose of the papillary muscles is to tense the chordae tendineae and mitral valve leaflets during ventricular systole.[35,36]

Abnormalities in the development of the mitral valve apparatus can result in hemodynamic and physiologic alterations in blood flow. When alterations in left-sided cardiac flow occur early in fetal development, the mitral valve may be hypoplastic or even atretic, with an accompanying small left ventricular cavity. The spectrum of mitral atresia and severe mitral hypoplasia is discussed in Chapter 78 on hypoplastic left heart syndrome.

Congenital Mitral Stenosis

Congenital mitral stenosis occurs when anomalous development of the mitral valve results in physiologic and anatomic obstruction to blood flow from the left atrium to the left ventricle. Other congenital anomalies of the valve, such as double-orifice mitral valve or parachute mitral valve, can also cause obstruction to left ventricular inflow. In the adult, the normal mitral valve orifice area is 4 to 6 cm^2. An orifice of 2 cm^2 usually causes mild symptoms of mitral stenosis, and a 1-cm^2 orifice often causes severe symptoms. Normal values in children are dependent on body surface area.[35]

The age at presentation of mitral stenosis is usually dependent on the severity of mitral valve obstruction. Often older patients present with symptoms of dyspnea on exertion. Elevation in heart

rate usually results in proportionately greater shortening of cardiac diastole, limiting left ventricular filling. Exercise requires a greater cardiac output, and as a result of tachycardia, cardiac ouptut generally decreases with exercise in patients with mitral stenosis. With severe mitral stenosis, cardiac output may be reduced even at rest. The left ventricular volume is decreased and cardiac function is generally normal. Severe mitral valve stenosis may be associated with endocardial ischemia and fibroelastosis of the left ventricle. The left atrium is enlarged and there is secondary pulmonary venous hypertension. In general, the fetal bronchocollateral circulation is adequate to prevent prenatal cardiac failure from mitral stenosis. Infants with severe mitral stenosis generally present with dyspnea, respiratory distress, mild cyanosis, failure to grow, and recurrent respiratory infections. Their presentation is similar to that of cor triatriatum. Systemic output and perfusion may be low. Right ventricular failure may develop because of pulmonary hypertension and pulmonary arteriolar vasoconstriction. Typically with congenital mitral stenosis, there is a normal to decreased S1 and increased pulmonary component of the second heart sound. An S4 is sometimes audible due to enhanced atrial systole. There is usually a long pandiastolic murmur audible at the cardiac apex. The right ventricular impulse is often increased to palpation. Hemoptysis and recurrent respiratory infections may complicate the clinical course of older children. Atrial fibrillation is relatively uncommon in children, although the development of atrial arrhythmias can further compromise cardiac output and potentiate the risk of development of left atrial thrombi.[37]

The chest roentgenogram in congenital mitral stenosis usually shows left atrial enlargement and signs of pulmonary venous congestion. The redistribution of pulmonary blood flow may be seen in older children with increased flow to the upper lobes. Kerley B-lines and pulmonary edema may also be present. The electrocardiogram generally shows left atrial or biatrial enlargement in sinus rhythm. Atrial fibrillation may be present. There is generally right ventricular hypertrophy with right-axis deviation.[37]

Echocardiographically, the mitral valve apparatus is visualized from the apical and parasternal long- and short-axis views. The valve leaflets appear thickened and rolled. There is fibrous interchordal obliteration. Abnormal chordal insertions and decreased papillary muscle distance or fusion of papillary muscles may be present. The left ventricular volume is usually 70 to 100% of normal. The orifice area can be calculated both angiographically and echocardiographically.[38,39] Doppler echocardiography is useful in determining the flow velocities across the mitral valve. The normal transvalvular mitral flow velocity is 64 to 92 cm/sec.[38]

At cardiac catheterization, arterial blood gases may show systemic desaturation as a result of pulmonary edema. The left atrial pressure, pulmonary venous pressure, and pulmonary arterial pressures are usually elevated. There is a gradient between the left atrial A wave and the left ventricular end-diastolic pressure. The anatomy of the mitral valve is best defined in the right and left anterior oblique projections. Associated mitral regurgitation may be present on left ventricular injection. Congenital mitral valve stenosis is sometimes associated with coarctation of the aorta, subaortic stenosis, and left ventricular endocardial sclerosis.[37]

If left untreated, the mean survival for congenital mitral stenosis is 3 yr. The preferred treatment is open surgical commissurotomy, although balloon dilation, both intraoperatively and during catheterization, has recently been attempted for acquired mitral valve stenosis in adults. Closed commissurotomy is still performed in some countries.[37] The commissurotomy must be viewed as a palliative procedure, since symptoms often recur 5 to 10 yr after commissurotomy. This may be secondary to failure of growth of the annulus or to restenosis. The risk of increasingly severe mitral regurgitation is also present. In addition, in younger patients, the prognosis is dependent on the left ventricular volume and the severity of associated anomalies. The mortality rate for mitral commissurotomy is approximately 1 to 3%, and for mitral valve replacement, 5 to 8%. Surgery is generally indicated for severe mitral valve stenosis if medical management fails, in symptomatic women who wish to become pregnant, in patients with refractory arrhythmias and congestive heart failure, and in patients with thromboembolic phenomenon or severe pulmonary hypertension. Whenever possible, mitral valve replacement should be avoided in young children, since anticoagulation is necessary, and ultimate replacement of the valve is generally required.[40–42]

Mild to moderate mitral stenosis can be managed by diuretic therapy, supplemental nutrition, and aggressive management of respiratory infections. Usually digoxin is not helpful unless arrhythmias are present or there is left or right ventricular failure. In patients with atrial fibrillation, anticoagulation should be considered before cardioversion if the arrhythmia has persisted for more than 3 to 4 wk. In general, cardioversion is successful in children, and sinus rhythm can be maintained with digoxin alone or with digoxin and a class 1A drug such as quinidine or procainamide. Rarely, amiodarone therapy is necessary to maintain sinus rhythm. Patients with incessant atrial fibrillation should be maintained on anticoagulant therapy to prevent thromboembolic development.[35,40–42]

The pulmonary hypertension generally associated with mitral stenosis may resolve incompletely or very slowly after operation. This may be secondary to persistent vasoconstriction. Pulmonary vascular obstructive disease is rarely seen as the result of pulmonary venous hypertension.[40–42]

Parachute Mitral Valve

Parachute mitral valve exists when all chordae insert in a single papillary muscle or in fused papillary muscles. The chordae are generally shortened. This cardiac defect is associated with Shone's complex, including supravalvar stenosing mitral ring, subvalvar aortic stenosis, and coarctation of the aorta. Parachute mitral valve has also been seen with ventricular septal defect, atrioventricular canal defect, or right ventricular outflow-tract obstruction.

Age at clinical presentation of patients depends on the degree of left ventricular inflow obstruction, but usually occurs before 10 yr. Survival appears to be correlated most closely with left ventricular size. If mitral stenosis is severe, this defect is often difficult to manage surgically without mitral valve replacement.

Double-Orifice Mitral Valve

Double-orifice mitral valve is an unusual congenital anomaly that can be found as an incidental autopsy finding associated with ventricular septal defect, endocardial cushion defect, bicuspid aortic or pulmonary valve, or coarctation of the aorta, or less commonly, Ebstein's malformation, subaortic stenosis, and secundum atrial septal defect. Although mitral valve function is usually nor-

mal, both mitral stenosis and mitral insufficiency have been reported with double-orifice mitral valve. Unlike parachute mitral valve, in double-orifice mitral valve, two papillary muscles are present. Multiple small papillary muscles may also be present. Two-dimensional echocardiography can usually delineate three leaflets. The orifices are usually anterior and posterior. The defect must be differentiated from cleft mitral valve in endocardial cushion defect where the cleft mitral valve appears as a defect in the anterior leaflet resulting in a two-sided mitral valve structure. Thickening of the leaflets may be seen in double-orifice mitral valve when stenosis or insufficiency is present.[43]

Mitral Valve Insufficiency

In pediatric patients, mitral valve insufficiency, or regurgitation of left ventricular blood into the left atrium during ventricular systole, usually develops as the result of acquired conditions. Acquired mitral insufficiency can develop secondary to myocarditis, congestive or hypertrophic cardiopulmonary, bacterial endocarditis, coronary insufficiency secondary to myocardial infarction or papillary muscle infarction, connective-tissue diseases or storage diseases affecting the cardiac muscle, rupture of the chordae tendineae or papillary muscles, annular dilatation, chronic rheumatic heart disease, or after a number of operations that involve the mitral valve.[35,44]

During mitral regurgitation, the left ventricle decompresses into the left atrium. Half of the regurgitant volume during systole occurs before the opening of the aortic valve. When the regurgitant volume exceeds the stroke volume, cardiac output decreases in the base-line state. In the normal left ventricle, the ejection fraction or shortening fraction is usually increased; normal or decreased left ventricular function may imply left ventricular cardiomyopathy.[45] The left ventricular wall stress and tension are decreased in mitral regurgitation; therefore the oxygen consumption in the left ventricle is not significantly elevated.[35,44]

Clinically, symptoms of mitral insufficiency are dependent on the severity of regurgitation, associated cardiac defects, left ventricular function, pulmonary artery pressure, and the rate of development of the regurgitation. Acute mitral regurgitation of moderate to severe degree is usually poorly tolerated and leads to acute pulmonary edema and respiratory distress. This is usually due to acquired rupture of the chordae tendineae or destruction of the atrioventricular valve. Chronic mitral regurgitation often results in diaphoresis, recurrent respiratory symptoms and infections, exercise intolerance, tachypnea, and failure to grow due to high caloric requirements.[35,44]

On cardiovascular examination, there is usually a diffuse left ventricular lift with a palpably enlarged heart. S1 is normal or decreased, and the pulmonary component of the second heart sound is either normal or increased. Mitral regurgitation causes a blowing apical high-pitched pansystolic murmur, which must be differentiated by its location and radiation from the murmur of tricuspid insufficiency. The murmur of mitral regurgitation radiates into the axilla and may be associated with a low-pitched diastolic flow rumble or third heart sound.

The electrocardiogram usually shows left atrial enlargement and left ventricular hypertrophy. Atrial fibrillation is uncommon in children. Chest roentgenography shows enlargement of the left atrial shadow, splaying of the right and left bronchi, and generalized cardiomegaly with left ventricular enlargement. The pulmonary vascular markings are increased and pulmonary edema or Kerley B-lines may be present.

Abnormal mitral valve appearance, valve motion, and chordal attachments can be assessed by two-dimensional echocardiography. Systolic left ventricular function is usually normal or increased. The degree of mitral regurgitation can be qualitatively assessed by color-flow Doppler mapping. This is generally accomplished by determining the width of the regurgitant volume and the penetration into the left atrium, and is graded as mild, moderate, or severe. The left atrial pressure can be quantitated in the absence of distal stenosis, by computing the difference in the systemic blood pressure and the gradient across the mitral valve, as determined by the regurgitant flow velocity.[45]

At cardiac catheterization, the arterial blood gases are usually normal, although mild systemic and left atrial desaturation can accompany pulmonary edema. Pulmonary capillary wedge pressure and pulmonary arterial pressure are often mildly elevated, but rarely as high as that seen in mitral stenosis. It is important to enter the left atrium in order to rule out pulmonary vein obstruction. Injections in the left ventricle and the anteroposterior and lateral or right/left anteroposterior oblique angulated views are best for demonstrating the degree of mitral insufficiency.[44]

Mild to moderate insufficiency can generally be managed by diuretic or digoxin therapy. Afterload reduction has been lifesaving for acute mitral regurgitation. However, long-term use of agents such as captopril is currently under evaluation. Certainly, afterload reduction may be of some benefit in children with moderate to severe regurgitation.

Indications for surgical intervention include symptomatic mitral regurgitation that is poorly controlled by medical management. Worsening cardiomyopathy or the steady decrease in left ventricular contraction indices over time may also be an indication for mitral valve replacement. The surgical treatment of choice is valvuloplasty or annuloplasty, although frequently mitral valve replacement is necessary. The Carpentier ring is frequently used for annuloplasty.[36,41]

Mitral Valve Replacement

All mitral valve prostheses are smaller than the mitral valve annulus that they replace. Valves are currently available in sizes from 17 to 32 mm. The most common prosthetic valve used in the mitral position, is a low-profile tilting disk prosthetic valve such as the St. Jude's or Medtronic valve. These valves have a low thrombogenicity rate of approximately 2% per patient per year. They have a larger effective orifice and more rapid ventricular filling rates than previously available valves. The bioprosthetic porcine valves previously used have shown rapid rates of calcification in children. These valves are currently considered for use only in young women of childbearing age.[46–49]

Patients with prosthetic valves in the mitral position require anticoagulation. Initially heparinization is used during the first 2 days after operation. Generally, this is accomplished with low-dose heparin. Partial thromboplastin times are measured before administration of heparin, immediately after the loading dose and at regular intervals during administration. The partial thromboplastin time should be maintained at 1½ to 2 times the control level. Once oral feedings have been established and a stable diet

is maintained, warfarin (Coumadin) can be administered orally daily. Warfarin is monitored by prothrombin times. The dose is adjusted to maintain a prothrombin time between 1½ and 2 times the control value. The prothrombin time generally shows little change after 24 hr and a slow rise by the third day. Maintenance warfarin doses will generally range from 5 to 10 mg/day in an adult patient. It may be helpful to use a 5-to-6-day overlap period between heparin and oral warfarin and heparin.[50–52] Aspirin and dipyridamole (Persantine) are inadequate for anticoagulation. Prosthetic mitral valve thrombosis has been documented with this regimen in a child with a St. Jude's prosthesis. Anticoagulation is continued permanently.

St. Jude's tilting-disk valves are radiotranslucent, except when photographed on end.[53] Their proper function can often be assessed by a combination of auscultation, two-dimensional Doppler echocardiography, and M-mode echocardiography.[54–56] It is useful to have a base-line echocardiographic study in the early perioperative period. If fusion of the disk leaflet or perivalvular leak is suspected, cardiac fluoroscopy or cardiac catheterization may be useful. Extreme caution should be used when crossing a prosthetic valve that may be dysfunctional. Catheter entrapment has been reported.[46]

Young women of childbearing age require special consideration. The risk of thromboembolic phenomena during pregnancy necessitates anticoagulation for prosthetic valves. Even the use of subcutaneous heparin during the first 3 mo of gestation has been associated with an 8.3% thromboembolic rate. Many of these women, however, did not have newer types of valves. The risk of warfarin embryopathy was found to be 7.9% in patients in whom warfarin was not discontinued before the first trimester of pregnancy. Prophylactic insertion of a porcine mitral valve may be considered in a young woman requiring operation, but often the valve does not require replacement at this age, and the planning of pregnancy is somewhat unpredictable. The prosthetic porcine valve allows only a 3-to-5-year period for childbirth, and the progressive development of calcific mitral stenosis may actually increase the risk of pregnancy. Currently, subcutaneous heparin is used during the first trimester and for 3 wk before delivery in patients on anticoagulation who are in New York Heart Association Class 1. Patients are generally informed of the statistical risk of complications of pregnancy, and it is discouraged in patients who are in New York Heart Association Class 2 or worse.

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CHAPTER 78

Hypoplastic Left Heart Syndrome

Gerald Barber

In 1952, Lev[1] first described the pathologic complex "hypoplasia of the aortic tract." This lesion included cases of: 1) isolated hypoplasia of the aorta, 2) hypoplasia of the aorta with ventricular septal defect, and 3) hypoplasia of the aorta with aortic stenosis or atresia with or without mitral stenosis or atresia. In 1958, Noonan and Nadas[2] referred to these lesions as "the hypoplastic left heart syndrome." While the pathologic complexes that result in the hypoplastic left heart syndrome are varied, the physiologic similarity of this collection of lesions has resulted in acceptance of this term. With the advent of surgical palliation for patients with hypoplastic left heart syndrome,[3–14] interest in a more precise anatomic definition of this collection of lesions has increased.

DEFINITION OF HYPOPLASTIC LEFT HEART SYNDROME

Hypoplastic left heart syndrome is a collective term describing a group of cardiac malformations in which there is aortic valve hypoplasia, stenosis, or atresia with either hypoplasia or absence of the left ventricle and, as a consequence, hypoplasia of the ascending aorta. This lesion is seen most frequently with severe mitral stenosis, mitral hypoplasia, or mitral atresia. The second most common association is with a common atrioventricular canal malaligned with regard to the muscular ventricular septum over the right ventricle. Cases involving transposition of the great arteries with hypoplasia of the left ventricle and pulmonary artery or hypoplasia of the right ventricle and aorta are not included in this group of malformations.

ANATOMY

Because hypoplastic left heart syndrome involves multiple pathologic entities, its anatomic manifestations are varied. Eighty-four percent of patients with hypoplastic left heart syndrome have aortic and mitral atresia, hypoplasia, or severe stenosis, while 16% have a malaligned atrioventricular canal.[15]

Aortic Atresia with Mitral Atresia

The anatomy of patients with aortic atresia (or virtual atresia) has been described thoroughly.[1,2,14,16–31] The inferior vena cava and right superior vena cava enter the right atrium normally. In 2.5 to 4.3% of patients there is a persistent left superior vena cava.[20,24] The right atrium is dilated (Fig. 78–1).[1,16–18,20,23,24] The tricuspid valve orifice is enlarged[15,23–25] with a mean circumference of 4.8 cm (normal circumference 3.4 cm).[23] The right ventricle is hypertrophied and enlarged.[17–19,23,24] In one study, right ventricular volume was three times normal.[23] The pulmonary orifice and main pulmonary artery are virtually always enlarged[15,17,18,20,23–25] and communicate with the descending aorta via the ductus arteriosus. Bharati[75] reported three cases of aortic atresia with pulmonary valve abnormalities (thickened nodular leaflets). Two of 126 cases of hypoplastic left heart syndrome presenting to the Children's Hospital of Philadelphia since 1985 have had concurrent pulmonic stenosis. The left and right pulmonary arteries arise from the underside of the main pulmonary arteries and may be larger than normal, normal in size, or smaller than normal.[25] In patients who die before reaching 2 weeks of age, there is no significant difference in the size and character of the small and medium-sized pulmonary artery branches.[14] In 2 out of 15 patients in this age

Fig. 78–1. Pathologic specimen from a child with hypoplastic left heart syndrome. The right atrium is dilated and the right ventricle hypertrophied. Severe endocardial fibroelastosis is present in the left ventricle (arrow). (Figure courtesy of P. Weinberg, MD.)

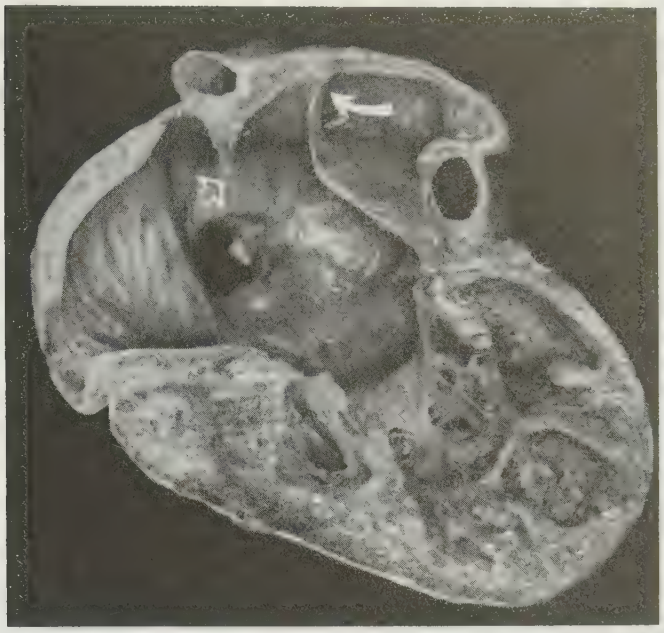

Fig. 78–2. Specimen from a child with hypoplastic left heart syndrome illustrating severe deviation of septum primum. The solid arrow points to the deviated attachment of septum primum from its normal attachment point (open arrow). Note how the gap between septum primum and septum secundum can be confused with a large unrestrictive atrial septal defect and how this arrangement in utero may limit systemic venous return to the left atrium. (Figure courtesy of P. Weinberg, MD.)

group and in all patients dying after 2 weeks of age studied by Sinha, there was medial hypertrophy of the pulmonary arteries.[14] Pulmonary venous connection is usually normal. Occasionally, there is anomalous or accessory pulmonary venous connection, usually through a persistent left vertical vein to a left innominate vein.[16] The left atrium is small and frequently hypertrophied.[16–18,20,23,24] An interatrial communication is usually present, although there may be a congenitally small foramen ovale.[16,17,24,27] In an autopsy series, 65% of patients had a posterior and leftward displacement of the superior attachment of septum primum relative to septum secundum (Fig. 78–2).[27]

Mitral stenosis or hypoplasia is present in approximately 60% of the cases while the remaining 40% have mitral atresia.[20,24] When there is mitral stenosis, the mitral valve leaflets are thickened with short thick chordae attached to short papillary muscles.[24] In cases with mitral atresia, there may be either a blind dimple on the floor of the left atrium at the usual site of the mitral valve with no grossly recognizable mitral valve tissue[17,18] or atretic mitral valve tissue.[30] The left ventricle does not form the apex of the heart. In cases with mitral hypoplasia or stenosis (patent left ventricular inflow), there is frequently prominent endocardial fibroelastosis (see Fig. 78–1)[1,14,20,22,24] with myofiber disarray,[31] focal calcification, and scarring of the myocardium. Evidence of early myocardial infarctions has been reported.[26]

In Bharati's study,[24] 87% of the patients with "hypoplastic left heart" had aortic atresia and 13% aortic stenosis while in Helton's study,[36] 61% had aortic atresia and 39% severe aortic stenosis. Of the 28 patients with aortic stenosis in Bharati's study,[24] 13 had a small bicuspid aortic valve, 7 had a small thickened tricuspid aortic valve that was normally divided, 2 had a small thickened incompletely divided tricuspid aortic valve, and 6 had a thickened unicuspid aortic valve. The coronary arteries originate normally from the aortic root and have a normal distribution.[24] The walls of the coronaries may be thicker than normal with multiple direct ventriculocoronary artery connections.[22] The clinical significance of these ventriculocoronary artery connections is as yet undetermined. The ascending and transverse aorta are hypoplastic. The typical figure of three contour of the upper descending aorta probably results from a juxtaductal ridge developing at a branch point of blood flow in the ductus arteriosus in utero.[32] With aortic atresia, the ascending aorta size is usually 1 to 3 mm. In rare cases with severe aortic stenosis, the mean ascending aorta size has been reported to be as large as 5 to 6 mm. Coarctation of the aorta is a common finding, which is present in 67 to 80% of the cases.[17,19,25,28,29]

Malaligned Atrioventricular Canal

The anatomic features of malaligned atrioventricular canal are similar to those of any atrioventricular canal defect. Atrial communication is via an ostium primum atrial septal defect. An inlet ventricular septal defect may or may not be present. The development of the left ventricle depends on the degreee of malalignment of the common atrioventricular valve. In cases with no or almost no inlet into the left ventricle (Fig. 78–3), left ventricular size is similar to that seen in patients with mitral atresia or stenosis. When part of the common atrioventricular valve enters the left ventricle, an intermediate size left ventricle is present. The left ventricle, however, still does not form the apex of the heart. Similarly, the size of the ascending and transverse aorta may be larger than in cases with aortic atresia but smaller than in patients with aortic stenosis.

Fig. 78–3. Short axis section through the heart of a child with a malaligned common atrioventricular canal. The small black arrows outline the common valve orifice while the larger black arrow points to the hypoplastic left ventricle. In this patient, none of the common valve emptied into the left ventricle. (Figure courtesy of P. Weinberg, MD.)

EMBRYOLOGY/ETIOLOGY

The embryologic cause of hypoplastic left heart syndrome is not known fully. Since hypoplastic left heart syndrome is a collection of lesions, there are probably multiple developmental anomalies that can lead to the syndrome. The most likely embryologic causes of hypoplastic left heart syndrome are either a limitation of left ventricular inflow or left ventricular outflow.

Left ventricular outflow obstruction may be the result of either severe aortic stenosis or atresia. When there is left ventricular outflow obstruction with an intact ventricular septum, the left ventricle is hypoplastic. In the rare case of left ventricular outflow obstruction with an unrestrictive ventricular septal defect, normal left ventricular development can occur. Thus, a primary myocardial abnormality is an unlikely cause of hypoplastic left heart syndrome. The resultant elevation in left ventricular pressure that occurs with patent left ventricular inflow (mitral stenosis) and obstructed left ventricular outflow in the absence of a ventricular septal defect probably causes the endocardiofibroelastosis seen in some cases of hypoplastic left heart syndrome. While a congenitally small or absent foramen ovale has been suggested as a possible cause of hypoplastic left heart syndrome,[24,46,47,48] this is more likely the result of increased left atrial pressure secondary to the left ventricular outflow obstruction. A primary abnormality of the aortic valve also might limit the development of the left ventricle in cases with a malaligned common atrioventricular canal. This may result in the atrioventricular valve appearing to be malaligned over the more normally developed right ventricle.

Theoretically, a displaced septum primum may limit left ventricular inflow by obstructing the normal shunting of inferior vena cava blood through the foramen ovale to the left ventricle. This decreased blood flow may result in a small left atrium, mitral valve, left ventricle, aortic valve, and ascending aorta. A displaced septum primum also may be present in some cases of hypoplastic left heart syndrome with malaligned common atrioventricular canal. Either this displacement of septum primum or the malalignment of the common atrioventricular valve may limit left ventricular inflow, resulting in a hypoplastic left ventricle, aortic valve and aortic arch.

Mitral stenosis, hypoplasia, or atresia is typically seen in hypoplastic left heart syndrome. Again, through limitation of left ventricular inflow, abnormalities of the mitral valve have been theorized as a primary cause of hypopoplastic left heart syndrome,[49–52] and experimentally a hypoplastic left ventricle can be produced in chick embryos by mechanical obstruction of the mitral valve.[53] Acquired mitral stenosis, however, frequently results in left atrial enlargement. Because patients with hypoplastic left heart syndrome have a hypoplastic rather than enlarged left atrium, congenital mitral stenosis probably is not a primary cause of hypoplastic left heart syndrome.

EPIDEMIOLOGY

Hypoplastic left heart syndrome has been reported to occur in at least 0.016% to 0.036% of live births.[37,38] In pathologic series, it represents 1.4 to 3.8% of congenital heart disease[39,40] and has been reported as causing 23% of the deaths due to the congenital heart disease in the newborn period.[16]

There is a slight male predominance in cases of hypoplastic left heart syndrome. Sixty to 70% of cases are reported to occur in males.[14,20,25] Currently, 57% of the patients with hypoplastic left heart syndrome seen at the Children's Hospital of Philadelphia are male. The recurrence risk for siblings of patients with hypoplastic left heart syndrome has been reported as 0.5% with a 2.2% risk for other forms of congenital heart disease.[37,41,42] Two genetic syndromes have been reported to have a high incidence of hypoplastic left heart syndrome. Three of 18 reported cases of duplication of the short arm of the twelfth chromosome had hypoplastic left heart syndrome[43] and Turner's syndrome has been detected in three patients with hypoplastic left heart syndrome seen at the Children's Hospital of Philadelphia.[44] Hypoplastic left heart syndrome has also been reported in one patient with a mosaic form of Turner's syndrome[45] and one patient with trisomy 18.[36] Single cases of hypoplastic left heart syndrome have been seen in patients with $4q^-$, $4p^-$, and $18p^-$ at the Children's Hospital of Philadelphia.

PHYSIOLOGY

Hypoplastic left heart syndrome patients have complex physiology. The left ventricle is essentially a nonfunctional structure. Pulmonary venous return must therefore pass to the right atrium. This occurs either through an atrial septal defect, a stretched foramen ovale or, rarely, by an anomalous pulmonary venous connection. In the right atrium, systemic and pulmonary venous return mix. The right ventricle must maintain both the pulmonary and systemic output, and the ductus arteriosus must remain patent for systemic perfusion. Perfusion is retrograde via the ductus arteriosus through the transverse arch and ascending aorta to the ca-

rotid and coronary arteries. With the left and right pulmonary arteries connected in parallel with the ductus arteriosus and descending aorta, the relative ratio of pulmonary to systemic blood flow depends on a delicate balance between pulmonary and systemic vascular resistances.

Prior to birth, oxygenation occurs via the placenta. Because the right ventricle is able to maintain systemic output via the ductus arteriosus, the child develops normally in utero.

After birth, oxygenation occurs in the lungs. Systemic blood flow is maintained as long as the ductus arteriosus remains patent. In the majority of cases, there is adequate systemic and pulmonary perfusion due to a balance between systemic and elevated pulmonary resistance. In some cases, however, there is a low pulmonary to systemic resistance ratio, resulting in excessive pulmonary blood flow. Although arterial oxygen saturation is elevated because of the high pulmonary blood flow, systemic perfusion is often marginal and the child frequently develops metabolic acidosis. In very rare cases, there is a high pulmonary-to-systemic resistance ratio. These patients appear markedly cyanotic because of inadequate pulmonary blood flow and acidotic because of inadequate oxygen delivery.

CLINICAL FEATURES

Historical Aspects

Because systemic perfusion and oxygenation are normal in utero, if the diagnosis is not made prior to birth by fetal echocardiography,[54,55] the child may be considered normal at birth.[2,16,17,26] Only 2 of 11 patients reported by Moodie[26] were in distress at birth; even so, distress was mild. When hypoplastic left heart syndrome presents within 24 hours of birth, it is usually because of severe obstruction to blood flow at the interatrial level (congenitally small or absent foramen ovale). More typically, however, Apgar scores are normal. Within 24 to 48 hours of birth, most patients with hyopoplastic left heart syndrome develop a dusky cyanosis with evidence of tachypnea and respiratory distress.[2,14,16,17,20] Watson,[16] however, reported that the onset of cyanosis and respiratory distress could be delayed for as long as 3 weeks. With ductal closure, the patient develops a metabolic acidosis. The mean pH at presentation prior to initiation of prostaglandins was 7.13 in one series[26] of 11 patients. Of 103 patients at the Children's Hospital of Philadelphia, the mean lowest preoperative pH was 7.22 ± 0.16 with a mean lowest preoperative bicarbonate concentration of 14 ± 5.5 mEq/L. Prostaglandin must be started at this stage to ensure patency of the ductus arteriosus if palliative surgery is to be considered. Both intravenous prostaglandin E_1 and oral prostaglandin E_2 have proven effective.[56–59]

Physical Examination

Physical examination typically reveals a mildy cyanotic child with tachypnea and tachycardia. Depending on the degree of ductal closure at the time of evaluation, peripheral pulses may be normal to diminished or absent. Watson[16] found diminished pulses in 32% of his patients whereas Sinha[14] reported diminished pulses in 60% of his patients. Rales may be heard, although generally the lung fields are clear. Cardiac examination reveals a dominant right ventricular impulse on palpation[16] with a decreased left ventricular (apical) impulse. S_1 is normal and S_2 is usually single and increased in intensity.[16] One-third of patients may have a gallop rhythm at the apex.[16] Fifty-eight to 67% of patients have a nonspecific soft grade 1/6 to 3/6 systolic murmur at the left sternal border[14,16,20] An apical middiastolic flow rumble is heard in 20% of the cases.[2,17] An early systolic ejection click may be heard in the rare patient with concurrent valvar pulmonic stenosis. Frequently, the liver is enlarged secondary to congestive heart failure.[16]

Electrocardiogram

The electrocardiogram (Fig. 78–4) frequently reflects the underlying pathology. Right atrial enlargement has been reported in 30 to 41%.[14,20] Watson[15] reported P waves that ranged from 0.5 to 4.0 mm with a mean of 2.5 mm in 27 patients. Two-thirds of his patients had a peaked P wave frontal plane. QRS axis is variable. Sinha[14] reported right axis deviation in 21 of 23 patients whereas Watson[16] reported a normal axis for age (mean +145 degrees) in 22 of 27 patients. Right ventricular hypertrophy is found in 78 to 92% of patients.[2,14,17] Approximately 56 percent of patients have a qR pattern in lead V_1 whereas 35% have either a rSR′ or pure R wave in lead V_1.[14,16] Q waves in the lateral precordial leads are seen in only 18% of patients.[16] Of patients, 36% are reported to have diminished left ventricular forces.[20]

In patients with malaligned common atrioventricular canal, the frontal plane QRS axis is leftward and superior.

Chest X-Ray

The chest x-ray in hypoplastic left heart syndrome (Fig. 78–5) is nonspecific. Cardiomegaly is reported in 75 to 85% of the patients.[14,20] In one series,[16] the cardiothoracic ratio varied from 0.54 to 0.68 with a mean cardiothoracic ratio of 0.62. The cardiac silhouette is described as globular (33%), rounded with a slight to moderate narrowing at the base (50%), or normal with a pulmonary artery bulge (17%).[16] Pulmonary vascular markings are increased in 68 to 82%.[14,20] In patients with a severely restrictive atrial septal defect, there may be a reticular pattern similar to that seen in total anomalous pulmonary venous connection with pulmonary venous obstruction.

Two-Dimensional and Doppler Echocardiography

Two-dimensional echocardiography is diagnostic in this lesion,[28,36,54,55,60–67] and its findings can have prognostic significance.[15]

All anatomic structures should be identified. Beginning with a transverse abdominal view, the inferior vena cava and abdominal aorta are identified and their relative positions noted. The hepatic veins and inferior vena cava should be followed to their entry into the right atrium. The intracardiac anatomy should be examined with subcostal frontal, sagittal, left oblique, and right oblique sweeps.[68–70] The relative sizes of the left and right atrium are recorded (Fig. 78–6). Pulmonary venous connection[71] should be established (Fig. 78–7). Because the pulmonary veins are usually enlarged due to pulmonary venous obstruction at the interatrial level, care must be taken not to confuse the pulmonary veins with the pulmonary arteries. Consistent with some obstruction at the interatrial level and an obligate atrial-level left-to-right shunt, the atrial septum is usually bowed from left to right. When the atrial septum is bowed from right to left, either severe tricuspid regurgitation or anomalous pulmonary venous connection should be suspected. When the atrial septum is thickened and severely bowed

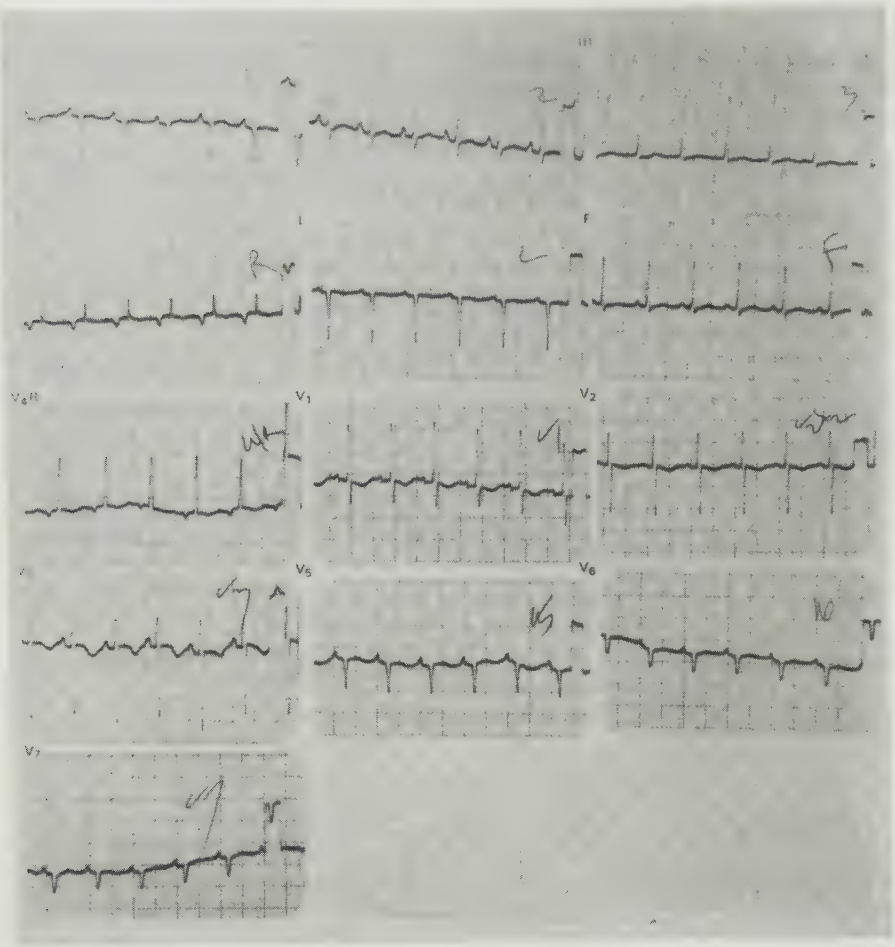

Fig. 78–4. Electrocardiogram in a child with hypoplastic left heart syndrome. "P" waves in lead II measure 2.5 mm. There are severe right axis deviation and right ventricular hypertrophy. Left ventricular forces are absent in leads V_5 through V_7.

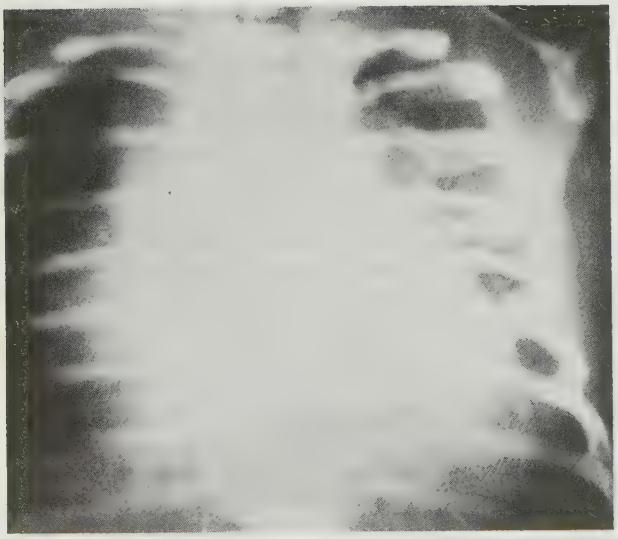

Fig. 78–5. Chest x-ray demonstrating cardiomegaly with increased pulmonary vascular markings in a child with hypoplastic left heart syndrome.

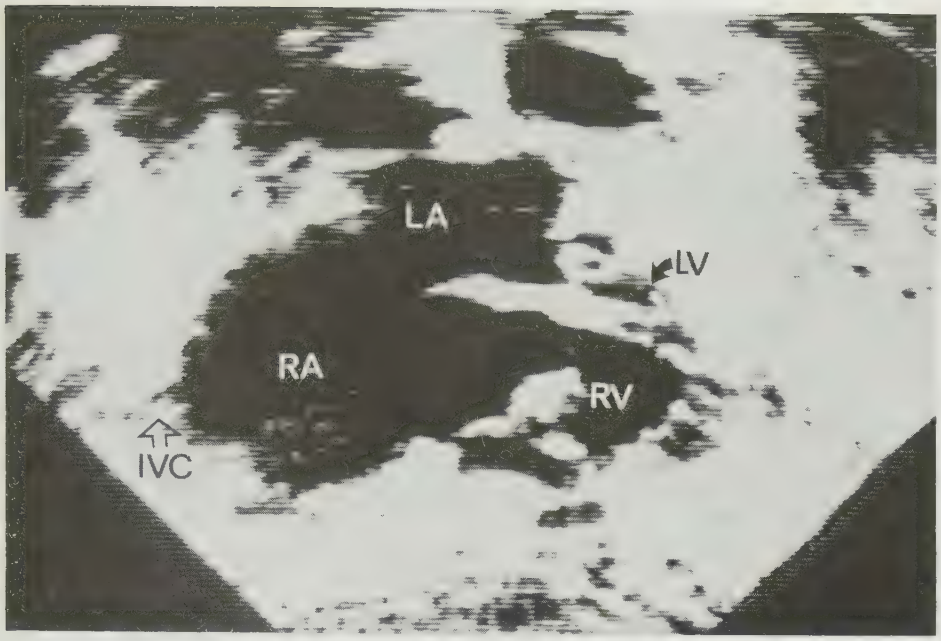

Fig. 78–6. Subcostal echocardiogram in a child with hypoplastic left heart syndrome illustrating the relative sizes of the left and right atria and ventricles. LA = left atrium, RA = right atrium, IVC = inferior vena cava, LV = left ventricle, RV = right ventricle.

from left to right (Fig. 78–8), a congenitally small or absent foramen ovale should be suspected. Septum primum should be examined for evidence of posterior and leftward deviation of its superior attachment.[36] In cases of mitral and aortic stenosis, the hypoplastic mitral valve, left ventricle and proximal ascending aorta should be characterized (Fig. 78–9). With mitral and aortic atresia, a left ventricle may not be visualized. The tricuspid valve (Fig. 78–10) should be evaluated for structural anomaly such as dysplasia or fusion and shortening of the chordae tendineae.[30] Right ventricular size and shortening can be assessed. The pulmonic valve should be evaluated for structural anomaly (Fig. 78–11). Following the right ventricular outflow tract, the ductus arteriosus and its connection with the descending aorta should be visualized.

In cases of malaligned common atrioventricular canal, an ostium primum atrial septal defect is visualized. The attachment of the common atrioventricular relative to the ventricular septum should be assessed (Fig. 78–12).

From suprasternal imaging, the anatomy of the ascending aorta, aortic arch, and upper descending aorta should be assessed using

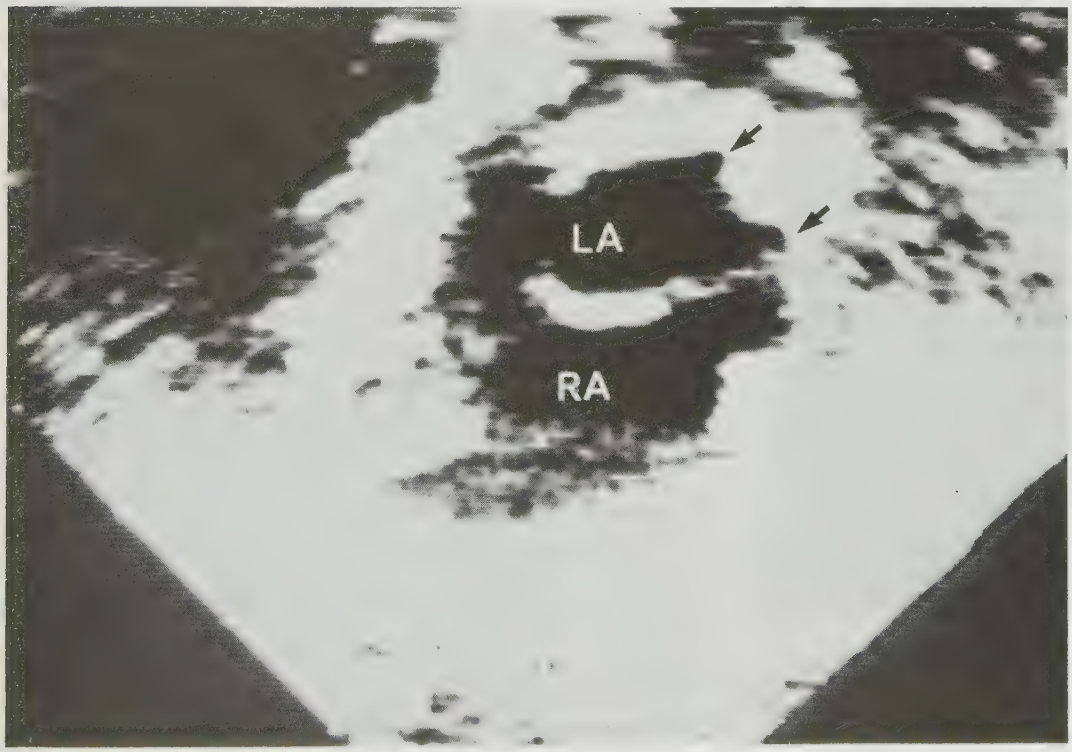

Fig. 78–7. Subcostal view demonstrating the entrance of the left pulmonary veins (arrows) into the left atrium. LA = left atrium, RA = right atrium.

Fig. 78–8. Subcostal view of a child with a congenitally absent foramen ovale. The left atrium is dilated. The atrial septum (arrow) is thickened and severely bowed from left to right. Blade/balloon septotomy was attempted after the left atrium was entered transseptally. Inadequate mixing at the atrial level persisted, and the child was operated on shortly thereafter. At operation, parts of the atrial septum measured greater than 1.0 cm. SVC = superior vena cava, LA = left atrium, RA = right atrium.

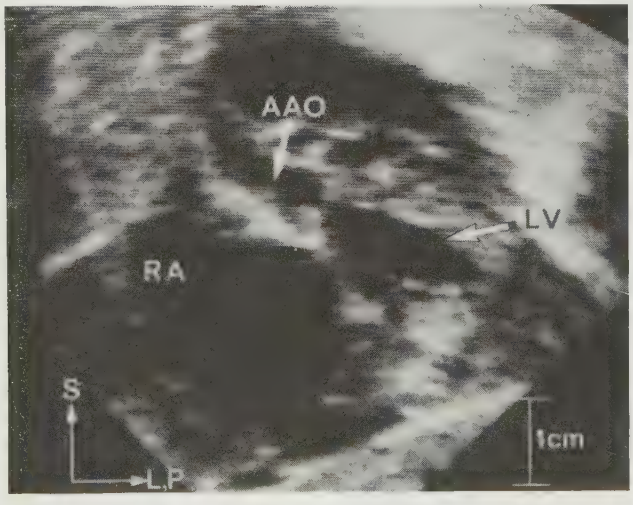

Fig. 78–9. Subcostal view demonstrating the hypoplastic ascending aorta arising from the small left ventricle. AAO = ascending aorta, RA = right atrium, LV = left ventricle, S = superior, L = left, P = posterior. (Figure courtesy of G. Helton, MD.)

frontal, sagittal, and left oblique views.[72] Continuity and size of the left and right pulmonary arteries are determined.

After the anatomic details are determined, color flow imaging, pulsed Doppler, and continuous wave Doppler are used to assess physiology. Of primary concern is the assessment of tricuspid or common atrioventricular valve regurgitation (Fig. 78–13).[15] Fifty-six percent of patients with hypoplastic left heart syndrome have tricuspid regurgitation preoperatively (35% mild, 16% moderate, and 5% severe).[15] The pulmonary valve then should be assessed to determine if there is any pulmonary stenosis.[75] If it is visualized, the mitral valve can be evaluated to determine whether it is stenotic or atretic. Similarly, the ascending aorta should be evaluated to determine whether the aortic valve is stenotic or atretic. The ductus arteriosus then should be evaluated to make sure it is not restrictive. The typical ductal flow pattern is a systolic flow from ductus to descending aorta with retrograde flow in the proximal descending aorta. During diastole, ductal flow is usually from aorta to pulmonary artery consistent with a lower pulmonary resistance than aortic resistance.[73] The absence of diastolic flow reversal into the ductus arteriosus suggests elevated pulmonary artery diastolic pressure usually due to a congenitally small or absent foramen ovale.

Cardiac Catheterization and Angiography

With accurate diagnosis possible by two-dimensional and Doppler echocardiography, cardiac catheterization is no longer routinely necessary in hypoplastic left heart syndrome.

Historically, cardiac catheterization has demonstrated superior vena cava oxygen saturations of 23 to 56%, right atrial saturations of 30 to 75%, with right ventricular and aortic saturations of 62 to 80%.[14] Mean left atrial pressure (25 mm Hg) is significantly

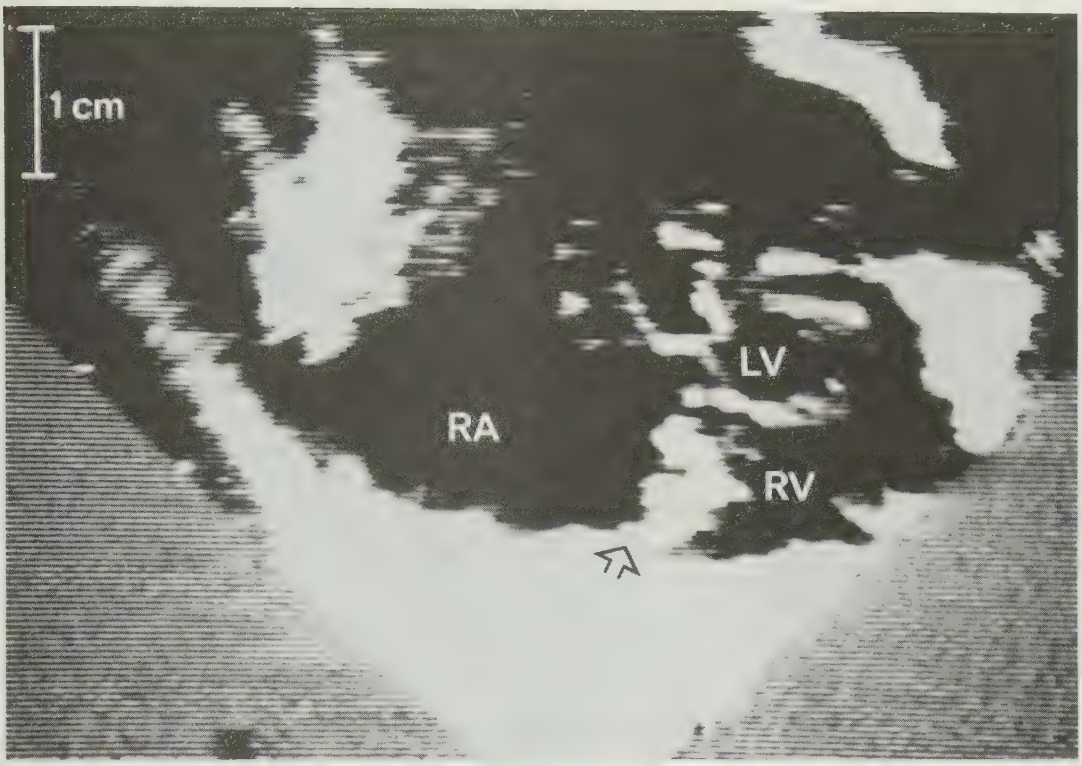

Fig. 78–10. Subcostal view demonstrating a thickened tricuspid valve (black arrow) in a child with hypoplastic left heart syndrome. The valve was bound down with short chordae and was severely regurgitant. RA = right atrium, LV = left ventricle, RV = right ventricle.

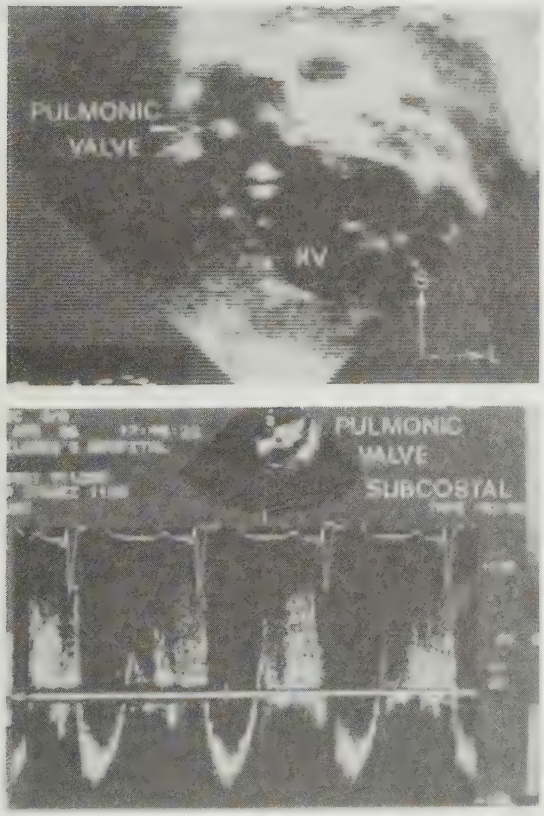

Fig. 78–11. Subcostal view of the right ventricular outflow tract and pulmonary valve (upper frame). The Doppler cursor is positioned below the pulmonary valve. In the lower frame, laminar systolic flow with turbulent diastolic regurgitant flow is demonstrated. RV = right ventricle, S = superior, L = left. (Figure courtesy of G. Helton, MD.)

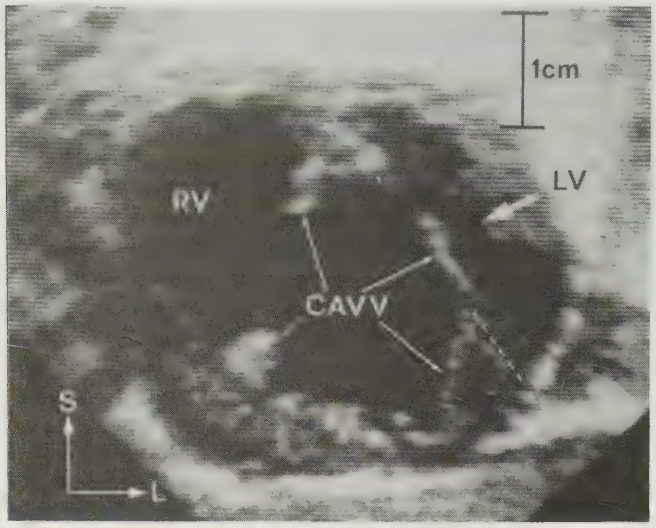

Fig. 78–12. Subcostal short axis in a patient with a hypoplastic left ventricle secondary to a malaligned common atrioventricular canal. The dotted line marks the plane of the ventricular septum. Arrows identify the orifice of the atrioventricular valve. The relative sizes of the right and left ventricles in this patient are illustrated. RV = right ventricle, LV = left ventricle, CAVV = common atrioventricular valve, S = superior, L = left. (Figure courtesy of G. Helton, MD.)

higher than mean right atrial pressure (12 mm Hg).[14] Right ventricular and pulmonary artery pressures are systemic.[14,20] Angiography on the right side (Fig. 78–14) of the heart reveals an enlarged right atrium, right ventricle and pulmonary artery.[17,20] The descending aorta is seen filling from the ductus arteriosus.[17] Injection in the descending aorta (Fig. 78–15) reveals the diminutive "string-like" ascending aorta.[16]

Hastreiter[76] attempted to validate catheterization measurements in hypoplastic left heart syndrome. In his study, he found that the right atrium was 1.6 times normal size, the tricuspid valve was 1.3 times normal size, the right ventricular diastolic volume was 1.8 times normal, the right ventricular systolic volume was 3.2 times normal, and the ascending aorta was 0.3 times normal size. While his autopsy measurements were uniformly smaller, presumably because of shrinkage, there was good correlation between angiography and autopsy measurements.

Because some obstruction to pulmonary venous return is beneficial by limiting pulmonary over circulation in patients with hypoplastic left heart syndrome, performing a balloon atrial septotomy during the cardiac catheterization may result in hemodynamic deterioration.

NATURAL HISTORY

The natural history of patients with hypoplastic left heart syndrome is uniformly poor. Untreated, over 95% of infants with hypoplastic left heart syndrome die within the first month of life.[77] Hypoplastic left heart syndrome accounts for approximately 25% of cardiac deaths during the first week and 15% of cardiac deaths during the first month of life.[2] Rarely, the ductus arteriosus remains patent. If pulmonary and systemic resistances are balanced, survival for 4 to 6 years has been reported sporadically.[13,78] One patient

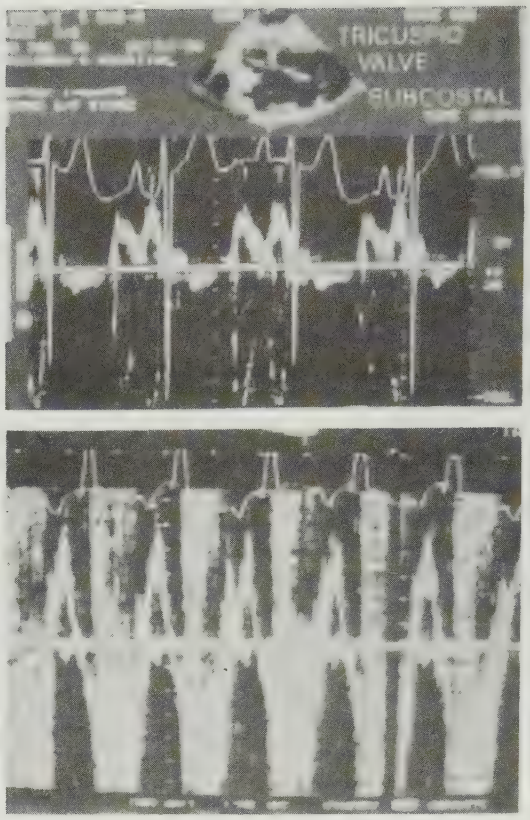

Fig. 78–13. Doppler signals obtained proximal to the tricuspid valve in hypoplastic left heart syndrome. The upper frame demonstrates normal laminar antegrade flow without evidence of tricuspid insufficiency. In the lower frame, there is turbulent systolic flow secondary to tricuspid insufficiency. (Figure courtesy of G. Helton, MD.)

at Texas Children's with pulmonary vascular disease survived to adolescence. These patients die from congestive heart failure, myocardial ischemia, and pulmonary vascular obstructive disease.

THERAPY

There is no medical treatment for hypoplastic left heart syndrome. The physician treating a patient with this disorder must decide whether or not to operate. Without surgery, survival is less than 5% at 1 year of age. With surgery, survival is 76% at 1 month and 61% at 1 year of age.[80] This survival rate is similar to that reported for surgery in other complicated forms of congenital heart disease such as pulmonary atresia with intact ventricular septum or truncus arteriosus. Historically, the surgical mortality for patients with pulmonary atresia with intact ventricular septum ranged from 20 to 65%.[81] Recently, early surgical mortality has been reported at 20 to 21%,[82,83] with late mortality of 21%.[82] In 1985, the Mayo Clinic reported their 15-year experience with truncus arteriosus;[84] surgical mortality there was 29%. Given the similarity of survival statistics between hypoplastic left heart syndrome, pulmonary atresia with intact ventricular septum and truncus arteriosus, the ethical issue of whether or not to operate also should be similar. Since most cardiologists and cardiovascular surgeons would not consider it ethical to withhold therapy from

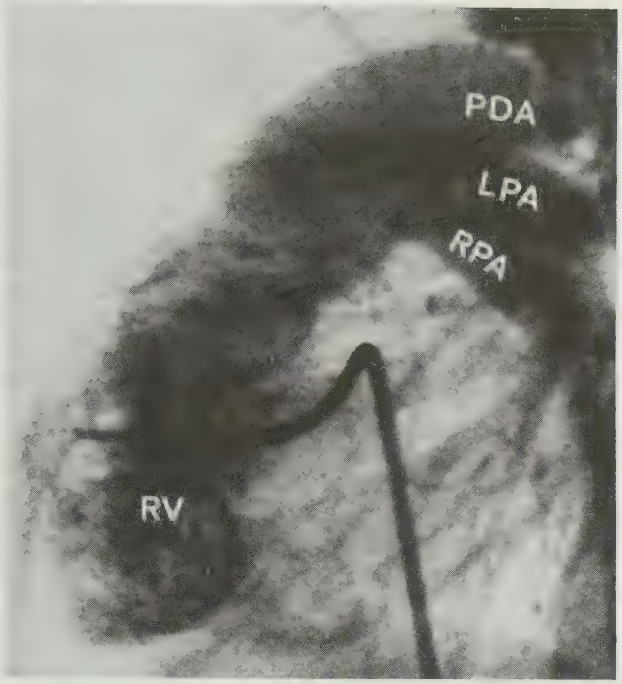

Fig. 78–14. Right ventricular angiogram in a child with hypoplastic left heart syndrome. Trabeculations consistent with a right ventricle are demonstrated. Both the left and right pulmonary artery and ductus arteriosus are visualized easily by the lateral projection. PDA = patent ductus arteriosus, LPA = left pulmonary artery, RPA = right pulmonary artery, RV = right ventricle.

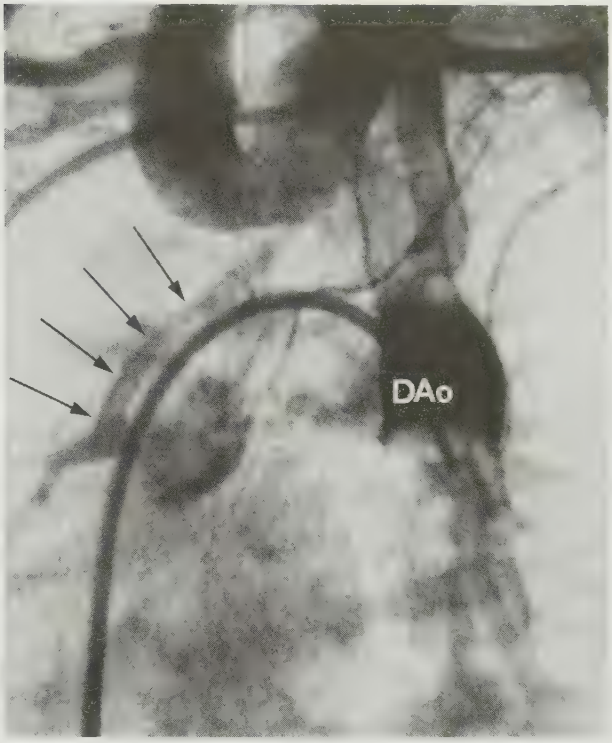

Fig. 78–15. Angiogram in a child with hypoplastic left heart syndrome demonstrating the hypoplastic ascending aorta (black arrows). The catheter is passed antegrade through the right ventricle, across the ductus arteriosus into the descending aorta. The descending aorta is balloon occluded and the injection made. DAo = descending aorta.

children with pulmonary atresia with intact ventricular septum and truncus arteriosus, it should be deemed equally unethical to withhold therapy from children with hypoplastic left heart syndrome.

Currently, there are two major surgical approaches for the hypoplastic left heart lesion. One operation involves reconstruction of the patient's own cardiovascular tissue in order to provide for hemodynamics compatible with life until a Fontan procedure can be performed whereas the second operation involves cardiac transplantation. The advantage of the reconstructive approach is the ability to use the patient's own tissue, thereby eliminating the need for immunosuppression; the advantage of the transplant is a two-ventricular repair.

Preoperative Care

The preoperative care of the child with hypoplastic left heart syndrome is the same regardless of the surgical approach chosen. When the diagnosis is made, the child should be started on prostaglandin E_1 intravenously at a dose of 0.05 to 0.10 micrograms/kilogram/minute. If available, orally administered prostaglandin E_2 may be used.[58,59] An arterial line should be inserted for monitoring of arterial oxygen saturation and acid–base status. If possible, the umbilical artery should be used to preserve the peripheral arteries for future use.

The major goal of the preoperative period is to assure adequate systemic perfusion for the child's metabolic needs. Systemic perfusion depends on a delicate balance between pulmonary and systemic vascular resistances. Usually the pulmonary resistance is less than systemic, and care must be taken not to further decrease pulmonary resistance. The chief metabolic factor that appears to influence pulmonary resistance in this group of patients is the P_{CO_2} level. For this reason, care must be taken not to hyperventilate these patients. Hyperoxic ventilation should be avoided. Patients with hypoplastic left heart syndrome often have no abnormality of oxygen transport across the alveolar membrane. The effect of supplemental oxygen is to decrease pulmonary resistance and increase systemic resistance, resulting in increased pulmonary blood flow and decreased systemic perfusion. While the oxygen saturation of peripheral blood may be higher, oxygen delivery is lower and metabolic acidosis ensues. Similarly, inotropic agents often result in an "unfavorable" pulmonary-to-systemic resistance ratio. While overall cardiac output may be increased, peripheral perfusion can decrease. Although they may be necessary in cases of hypoplastic left heart syndrome with additional problems such as sepsis, inotropic agents are usually unnecessary and harmful in uncomplicated cases of hypoplastic left heart syndrome. Once the pulmonary vascular resistance has decreased to a low level, it is often difficult to stabilize the systemic perfusion. One way to increase pulmonary resistance—and thus systemic perfusion—in these patients is to electively intubate and paralyze them. The child can then be hypoventilated to a P_{CO_2} of 45 to 50 mm Hg. This elevates pulmonary resistance and increases peripheral perfusion.

Some degree of pulmonary venous obstruction—usually at the level of a patent foramen ovale or atrial septal defect—is a frequent component of elevated pulmonary resistance in this lesion. Mild

to moderate interatrial obstruction benefits preoperative hemodynamics. Unless the P_{O_2} is less than 25 mm Hg, atrial septotomy should not be performed prior to surgical palliation.

In the rare case of hypoplastic left heart syndrome with a congenitally small or absent foramen ovale, there may be so much obstruction to pulmonary venous drainage that inadequate pulmonary blood flow results. In contrast to other patients with hypoplastic left heart syndrome, these patients have a low peripheral oxygen saturation. These patients also have no diastolic reversal in their ductus arteriosus on the preoperative Doppler echocardiogram. Such patients may require emergency surgery as it may be impossible to either stabilize them medically or to perform an adequate blade/balloon septotomy in the cardiac catheterization laboratory.

Neonatal problems must be recognized and treated. Since prostaglandin E_1 or E_2 can maintain patency of the ductus arteriosus, there is usually no need to rush a hemodynamically unstable child to the operating room. While it is logical to blame hemodynamic and metabolic abnormalities on the child's cardiac disease, sepsis always must be considered. In the presence of any evidence for sepsis, appropriate cultures should be performed and the child should be started on antibiotics pending culture results. The antibiotics chosen should be based on the sensitivities of organisms associated with neonatal sepsis in that institution. If the child is infected, surgery should be delayed until the infection is resolved. Renal and hepatic failure due to poor systemic perfusion should be recognized and treated. Necrotizing enterocolitis may occur due to decreased bowel wall perfusion.

Because of the association with Turner's syndrome, a karyotype should be obtained in all females with hypoplastic left heart syndrome. Due to the link between hypoplastic left heart syndrome and partial chromosomal deletions, a karyotype also should be obtained in males with any other somatic abnormality along with hypoplastic left heart syndrome.

Reconstructive Approach: First Stage

The first stage of the reconstructive approach for hypoplastic left heart syndrome (Fig. 78–16) is a surgical technique that uses native cardiovascular tissue to palliate this lesion. Since first described in 1980,[10] this technique has undergone many modifications. The goals of the first stage of the reconstructive approach are to assure systemic perfusion in the absence of a ductus arteriosus and to protect the pulmonary vascular bed for an ultimate modified Fontan[79] operation.

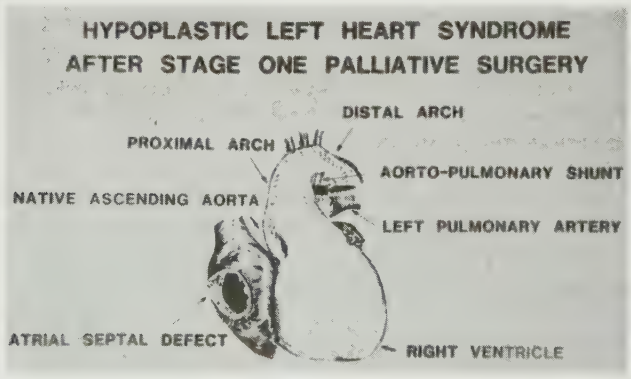

Fig. 78–16. Diagram of the first stage of the reconstructive approach for hypoplastic left heart syndrome. (Figure courtesy of W. Norwood, MD, as modified by G. Helton, MD.)

The first-stage palliative operation is initiated by induction of anesthesia with fentanyl and pancuronium. The radial artery is then cannulated. A midline sternotomy is performed and the thymus excised. After cannulation of the pulmonary artery distal to the sinuses of Valsalva and the right atrial appendage, cardiopulmonary bypass is begun. The infant is then cooled to 20° Celsius. The left and right pulmonary arteries are exposed and occluded with 2-0 Tevdek tourniquets. The brachiocephalic vessels are exposed and looped with 2-0 Tevdek tourniquets. The aortic arch is then dissected into the posterior mediastinum. The brachiocephalic vessels are occluded and circulatory arrest begun. After removal of the arterial and venous cannulae, cardioplegia solution is perfused through the pulmonary artery cannulation site. The descending thoracic aorta is then temporarily occluded and septum primum excised through the venous cannulation site. At the site of the takeoff of the right pulmonary artery, the pulmonary artery is transsected and the distal stump oversewn. A patch is used for this to avoid distortion of pulmonary artery anatomy. The ductus arteriosus is exposed and ligated. It is transsected at the aortic end. The aortic arch is then incised from 2 cm distal to the insertion of the ductus arteriosus to the level of the transsected pulmonary artery. The junction of the aortic isthmus is gusseted with a patch to minimize the development of late distal arch obstruction. A short, 4 mm shunt is then constructed from the underside of the augmented aortic arch to the branch pulmonary arteries. The pulmonary homograft is then carried around the aortic arch and the anastomosis finished by joining the proximal pulmonary artery and the pulmonary homograft with the ascending aorta. Cardiopulmonary bypass is reinstituted and the patient warmed. The patient is then weaned from cardiopulmonary bypass, a pressure monitoring line placed in the right atrium, and then transported to the intensive care unit.

Actuarial survival for this approach is currently 76% at 1 month and 61% at 12 months.[80] It is anticipated that with further identification of potential problems and refinement of techniques, the survival statistics will continue to improve.

Postoperative Management

Early

In the immediate postoperative period, therapy changes. Instead of hypoventilation to decrease pulmonary blood flow, the child should be hyperventilated to a P_{CO_2} between 20 and 30 mm Hg to decrease pulmonary vascular resistance. The child should be weaned from mechanical ventilation and extubated as soon as tolerated. Frequently, this takes 4 to 6 days.

Oral feeding should begin as soon as possible. Because children with hypoplastic left heart syndrome may not have been fed orally prior to surgery, sucking may be delayed. Oral intake may be supplemented by nasogastric gavage feeding. If the child is otherwise recovered from surgery, consideration should be given to teaching the parents the techniques of home gavage feeding.

Late

After the child is discharged, regular cardiovascular evaluations are essential for early detection of potential complications.

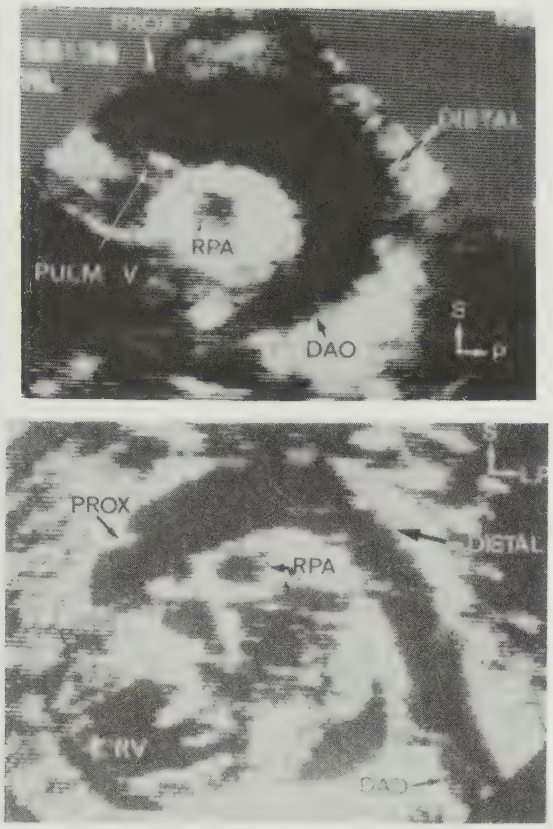

Fig. 78–17. Suprasternal (upper frame) and subcostal (lower frame) imaging of the reconstructed aortic arch in a child without postoperative arch obstruction. Prox = proximal anastomosis, Distal = distal anastomosis, Pulm V = pulmonary vein, RPA = right pulmonary artery, DAO = descending aorta, S = superior, P = posterior, L = left, RV = right ventricle. (Figure courtesy of G. Helton, MD.)

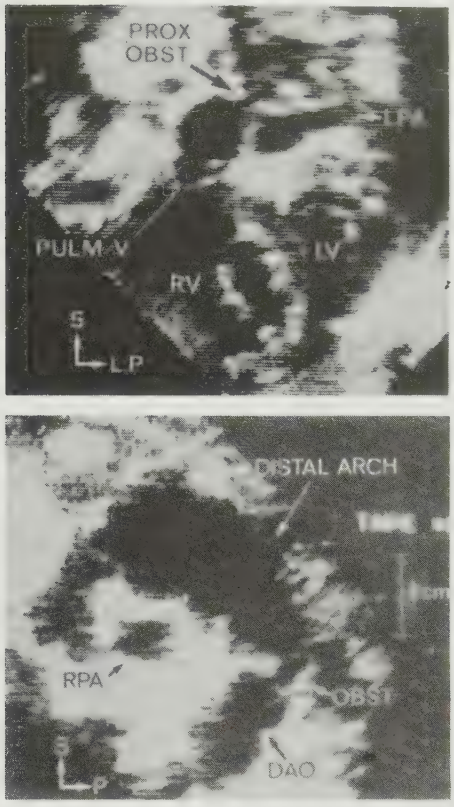

Fig. 78–18. The echocardiographic appearance of proximal and distal arch obstruction after palliation of hypoplastic left heart syndrome is apparent when the upper and lower frames of this figure are compared to those of Figure 78–17. Obst = site of obstruction, LPA = left pulmonary artery, LV = left ventricle. The other abbreviations are the same as for Figure 78–17. (Figure courtesy of G. Helton, MD.)

Aortic arch obstruction can occur at two sites: the commonest site is in the distal arch; the other is the proximal, threeway, anastomosis between the proximal main pulmonary artery, the homograft gusset, and the ascending aorta. While the incidence of arch obstruction has diminished, immediate recognition of it is critical for the child's well-being. In hypoplastic left heart syndrome after the first stage of the reconstructive approach, the right ventricle is volume loaded and pumps systemic pressure. Any concurrent extra pressure load results in rapid deterioration of right ventricular systolic performance. Physical examination is often misleading in the detection of arch obstruction. Because there is an obligatory run-of through the systemic-to-pulmonary shunt, the femoral pulses appear normal or nearly normal to palpation. Furthermore, the typical gradients are 25 mm Hg. It appears that the right ventricle usually decompensates long before a large pressure gradient is attained. Two-dimensional echocardiography with suprasternal imaging of the arch (Figs. 78–17 and 78–18) and sequential pulsed Doppler interrogation of multiple points (Figs. 78–19, 78–20, and 78–21) along the reconstructed aorta, however, has proven reliable in detecting arch obstruction after the first stage of the reconstructive approach.[85] Color Doppler has facilitated the assessment of the aortic reconstruction and allows more optimal alignment of the continuous wave Doppler cursor. If two-dimensional and Dopper echocardiography suggests arch obstruction, cardiac catheterization should be performed to confirm this and surgical relief undertaken without delay.

Another potential complication is the development of rapidly progressing cyanosis. Usually, this is due to limited perfusion through the shunt, although rarely cyanosis may occur secondary to an inadequate atrial septal defect (Fig. 78–22). While blade and balloon atrial septotomy have been attempted to increase the opening in the interatrial communication, they are rarely successful and a second surgical septectomy frequently is performed. Fortunately, this complication usually can be avoided by recognition of the variations of atrial septal morphology[36] and by performing an extensive initial surgical septectomy.

Tricuspid regurgitation can develop or persist. Significant tricuspid regurgitation is poorly tolerated by the already volume-loaded ventricle. Because of this and the fact that there is no significant change in the degree of tricuspid regurgitation from the preoperative period through the late postoperative period,[74] survival following the first stage of the reconstructive approach has been correlated to the degree of tricuspid regurgitation preoperatively.[15] Tricuspid annuloplasty or valve replacement may be required in cases with moderate to severe tricuspid regurgitation.

Mild regurgitation of the native pulmonary valve (neoaortic

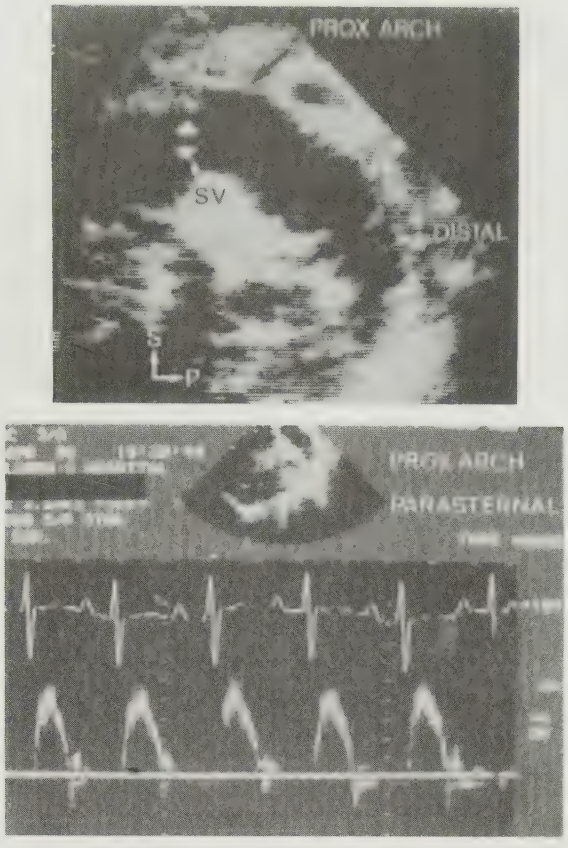

Fig. 78–19. Two-dimensional image (upper frame) and Doppler flow signal (lower frame) of the ascending aorta after first-stage palliation for hypoplastic left heart syndrome. Laminar antegrade flow without diastolic reversal is seen in the lower frame. SV = site of sample volume, Prox arch = proximal aortic arch, Distal = distal aortic arch, S = superior, P = posterior. (Figure courtesy of G. Helton, MD.)

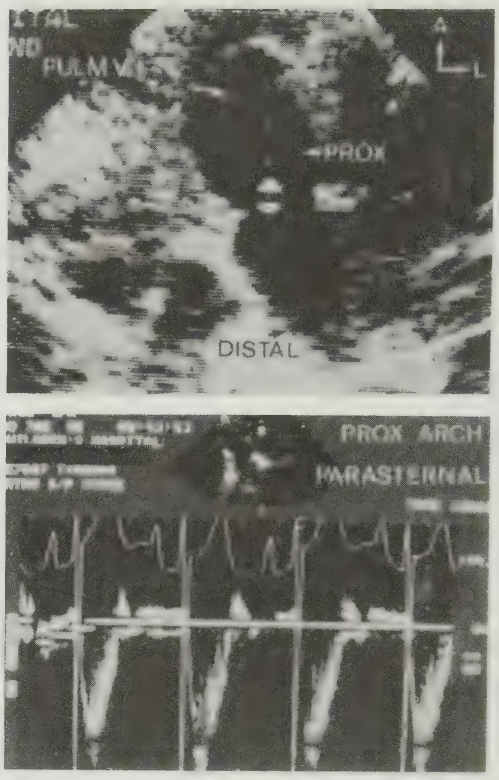

Fig. 78–20. The upper frame shows the position of the Doppler sample volume, which has now been moved to the site of the proximal anastomosis. Unobstructed laminar flow is seen in the lower frame. Pulm V = pulmonary vein, A = anterior, L = lateral, Prox = proximal anastomosis, Distal = distal anastomosis. (Figure courtesy of G. Helton, MD.)

valve) has been detected postoperatively by Doppler echocardiography but has not proven clinically significant.

In our early experience, evaluation by echocardiography (Figs. 78–23 and 78–24) occasionally revealed a disparity in the size of the left and right pulmonary arteries. In an effort to induce a more equal development of the pulmonary arteries and to allow for more favorable Fontan hemodynamics, the systemic-to-pulmonary shunt was changed from a modified right Blalock-Taussig shunt to a more centrally placed shunt. The relative sizes of the left and right pulmonary arteries should be assessed both echocardiographically and angiographically prior to the second stage of the reconstructive approach.

After the first stage reconstruction of hypoplastic left heart syndrome, the electrocardiogram remains relatively unchanged (Fig. 78–25). While the amplitude of the P-wave in lead II may decrease from the preoperative amplitude, typically right axis deviation with right ventricular hypertrophy and diminished R waves in the lateral precordial leads persists.

The chest x ray continues to show cardiomegaly after the first stage of the reconstructive approach for hypoplastic left heart syndrome. Pulmonary vascular markings are decreased relative to the preoperative chest roentgenogram.

Cardiac catheterization should be performed prior to the second stage of the reconstruction. The purpose of this catheterization is the same as in any pre-Fontan evaluation of a patient with single ventricle. Pulmonary resistance should be evaluated. Preferably, pulmonary artery pressure is measured directly with a catheter placed retrograde through the shunt. Occasionally the shunt cannot be entered. In these cases, pulmonary venous wedge pressures may be used. Right ventricular function is assessed by measurement of the end diastolic pressure. Usually, the right ventricular end diastolic pressure is about 7 to 8 mm Hg and the pulmonary artery resistance less than 2.5 Wood Units M^2. Routinely, two angiograms are performed. The first is a retrograde angiogram in the right ventricle filmed AP and lateral (Fig. 78–26). This defines ventricular morphology and demonstrates any tricuspid regurgitation that may be present. The second angiogram is in the midportion of the ascending aorta (Fig. 78–27). This angiogram is filmed AP with 30 degrees of cranial angulation and lateral. The cranial angulation is used to clarify the pulmonary artery anatomy. If the pulmonary arteries are entered through the shunt, a small volume injection is performed in the pulmonary arteries to define their anatomy.

Reconstructive Approach: Second Stage

The second stage of the reconstructive approach for hypoplastic left heart syndrome is a modified Fontan procedure.[79] In order to limit the amount of time the right ventricle is subjected to a volume

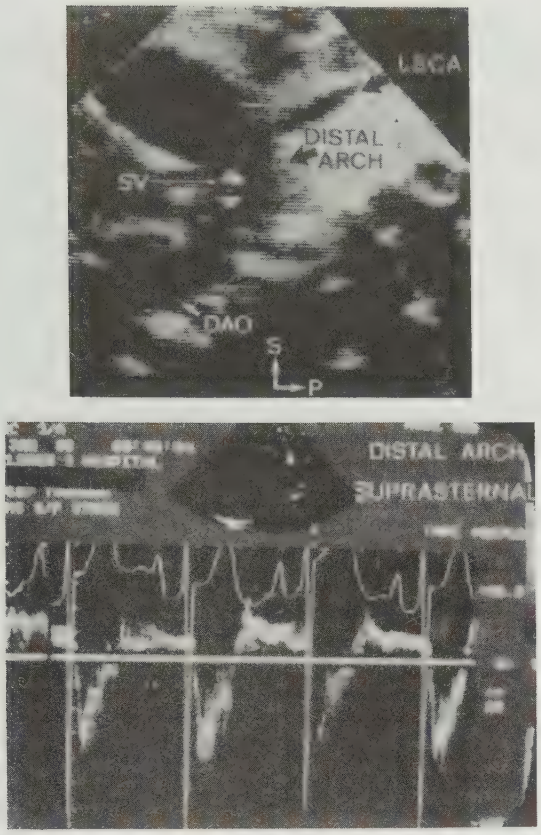

Fig. 78–21. The sample volume is now positioned at the site of the distal aortic anastomosis (upper frame). Laminar forward systolic flow with diastolic reversal into the systemic to pulmonary artery shunt is seen in the lower frame. SV = sample volume, LSCA = left subclavian artery, DAO = descending aorta, S = superior, P = posterior. (Figure courtesy of G. Helton, MD.)

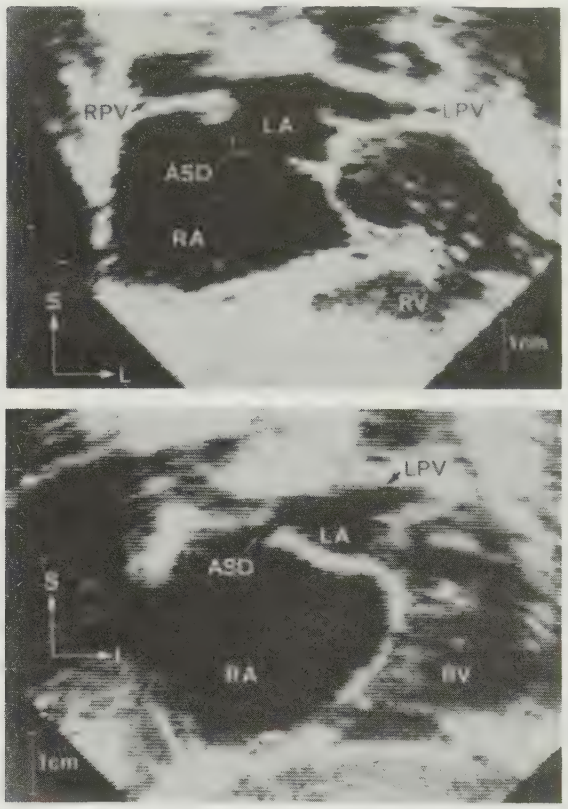

Fig. 78–22. Subcostal echocardiographic imaging in two children with hypoplastic left heart syndrome. A widely patent atrial septum is demonstrated in the upper frame. The lower frame demonstrates a restrictive atrial septal defect. The left pulmonary vein is dilated in the child with the restrictive ASD. RPV = right pulmonary vein, LPV = left pulmonary vein, LA = left atrium, ASD = atrial septal defect, RA = right atrium, RV = right ventricle, S = superior, L = left. (Figure courtesy of G. Helton, MD.)

and pressure load, this operation is performed at approximately 18 months of age.

The heart is exposed through a midline sternotomy and cardiopulmonary bypass begun through ascending aorta and right atrial appendage cannulation sites. The systemic to pulmonary shunt is exposed and occluded and the patient cooled to 20° Celsius. The aorta is then cross-clamped, cardioplegia infused, and circulatory arrest begun. The pulmonary arteries are widely incised from the right superior vena cava to the takeoff of the left lower lobe branch. The right atrium is then incised from the sulcus terminalis to the insertion of the eustachian valve inferiorly. The interatrial communication is enlarged, if possible, and an incision is made in the dome of the right atrium adjacent to the right pulmonary artery and carried into the posterior aspect of the right superior vena cava. A suture line is then begun at the posterior aspect of the right superior vena cava and the right pulmonary artery. Inferior vena cava blood flow is baffled from the inferior vena cava–right atrial junction to the junction of the superior vena cava with the pulmonary artery using half of a 10 mm diameter Gore-Tex tube. This baffling technique minimizes obstruction of the pulmonary venous channel, which occasionally occurred when the pulmonary veins were instead baffled to the tricuspid valve. The roof of the anastomosis between the systemic venous channel and the pulmonary arteries is then formed with a pulmonary homograft. The pulmonary homograft is extended along the remaining length of the pulmonary artery incision to ensure a widely patent communication into both the left and right pulmonary arteries. The patient is then returned to cardiopulmonary bypass, warmed, and weaned from bypass. Monitoring catheters are placed in the pulmonary artery and pulmonary venous channel, and the child is brought to the intensive care unit.

Postsurgical management is similar to that for any patient after a modified Fontan procedure. A follow-up cardiac catheterization is recommended 1 year postoperatively to assess hemodynamics.

Twenty-nine patients underwent the second stage of the reconstructive procedure for hypoplastic left heart syndrome from October 1984 through January 1987. Early mortality was 9/29 (31%) with 1 late death among the 20 survivors (7%).

Heart Transplantation

Yacoub first attempted heart transplantation for hypoplastic left heart syndrome in 1984. Shortly thereafter, Bailey[6] performed a baboon-to-human cardiac xenotransplantation for hypoplastic left heart syndrome. This child survived 20 days. In 1986, Bailey[5] reported his technique for orthotopic cardiac xenotransplantation for hypoplastic left heart syndrome. Although a baboon donor was

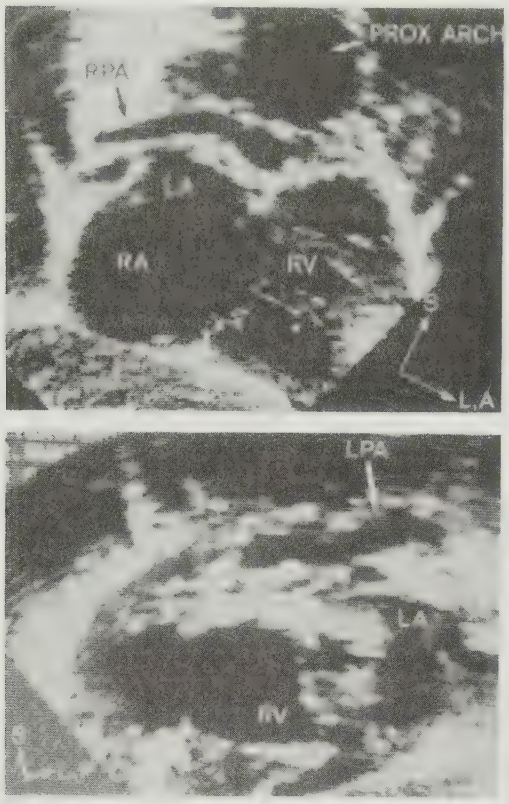

Fig. 78–23. Normal development of the right (upper frame) and left (lower frame) pulmonary arteries is seen in these subcostal images from a child with hypoplastic left heart syndrome after first-stage palliative repair. RPA = right pulmonary artery, LA = left atrium, RA = right atrium, RV = right ventricle, Prox arch = proximal arch, LPA = left pulmonary artery, S = superior, L = left, P = posterior, A = anterior. (Figure courtesy of G. Helton, MD.)

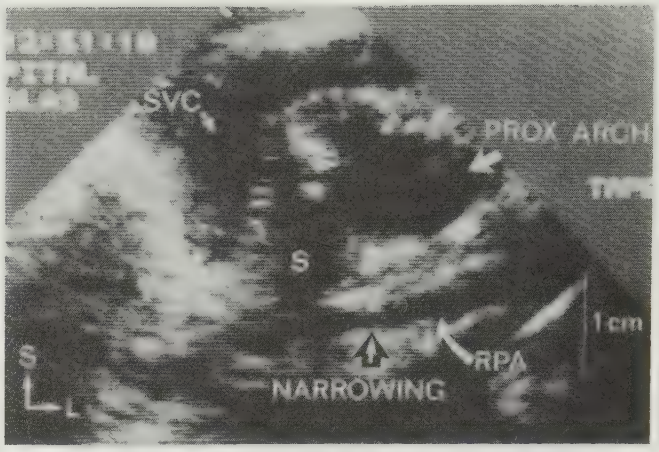

Fig. 78–24. Suprasternal two-dimensional echocardiogram demonstrating narrowing in the right pulmonary artery medial to a modified right Blalock-Taussig shunt. SVC = superior vena cava, Prox arch = proximal arch, S = shunt, RPA = right pulmonary artery. Superior and leftward directions are indicated by the direction arrows. (Figure courtesy of G. Helton, MD.)

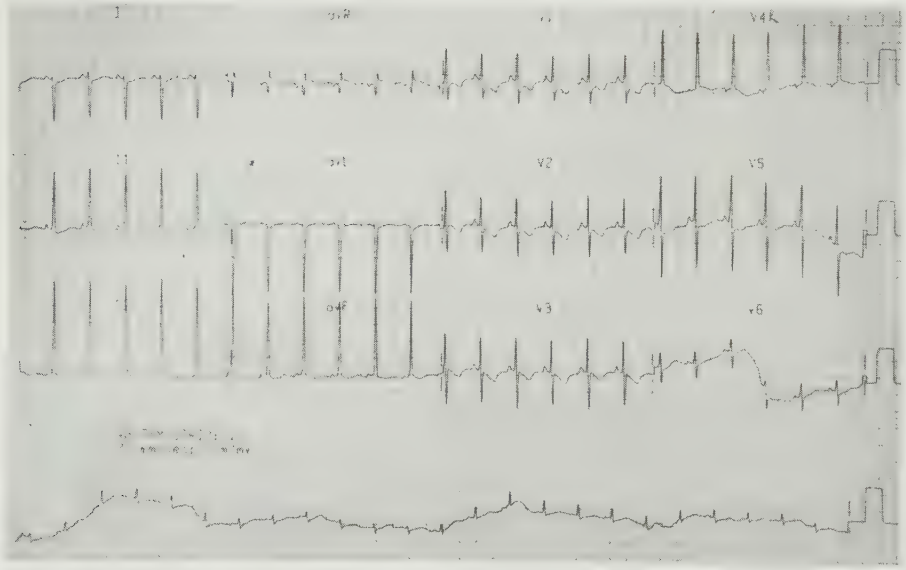

Fig. 78–25. Electrocardiogram obtained prior to the second-stage palliative operation for hypoplastic left heart syndrome. Right axis deviation and right ventricular hypertrophy are present. The R/S ratio in lead V_6 remains less than 1.

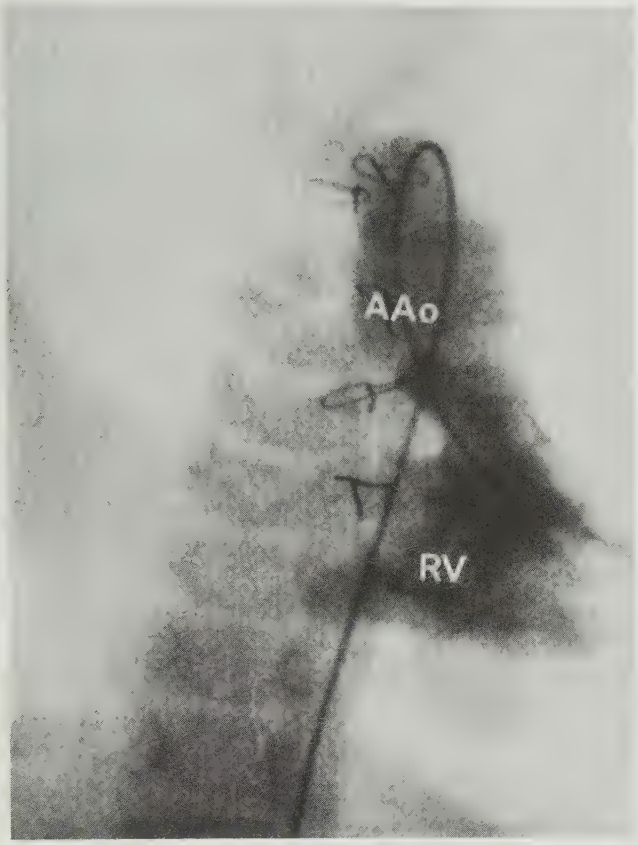

Fig. 78–26. Retrograde right ventricular angiogram after first-stage palliative repair of hypoplastic left heart syndrome. No tricuspid regurgitation is visualized. The ascending aorta anastomosis is widely patent. AAo = ascending aota, RV = right ventricle.

used, the donor source (allograft verus xenograft) should have no influence on the technical aspects of the operation.[6]

The child is anesthetized with a narcotic and paralyzing agent. Then heparin, methylprednisolone, and cefamandole are given, and surface cooling begun. The chest is opened with a midline sternotomy, and a near-total thymectomy is performed. Aortic arch branches are loosely snared. Extracorporeal perfusion is begun utilizing cannulation sites in the right atrium and ductus arteriosus. A snare is tightened around the ductal cannula, and the child is cooled to 20° Celsius. The arch vessel snares are tightened and bypass discontinued. The heart is then excised, leaving the posterior atrial walls and septum in place. The main pulmonary artery is transected at the bifurcation of the left and right pulmonary arteries. The ascending aorta is then ligated and transected just proximal to the brachiocephalic trunk. The ductus arteriosus is then removed from the underside of the descending aorta and the aorta incised from the brachiocephalic trunk to several millimeters beyond the ductus insertion site. The donor heart is inserted and sutured to the atrial remnant. Donor and recipient aortas are anastomosed, since the donor's aortic arch was beveled previously to match the incision in the recipient's arch. Donor and recipient pulmonary arteries are then anastomosed. Cardiopulmonary bypass is restarted. The child is warmed and weaned from bypass.

In 1986, Bailey[4] reported his results with cardiac allotransplantation for hypoplastic left heart syndrome. To date, 17 patients

Fig. 78–27. Retrograde angiogram in the ascending aorta after first-stage palliative repair. A right modified Blalock-Taussig shunt is visualized (arrow) with filling of the pulmonary arteries. Note the large size of the reconstructed ascending aorta after the first-stage reconstructive approach.

with hypoplastic left heart syndrome have been accepted into the transplant program at Loma Linda University Medical Center. Ten of these patients died awaiting a donor, and 2 died in the perioperative period. The 5 remaining children are doing well 3 to 18 months postoperatively.[86]

CONCLUSION

Over the last decade, well-defined surgical options have been developed for patients with hypoplastic left heart syndrome. The challenge for the future is to characterize this group of lesions better so that the preoperative, operative, and postoperative management may be further improved.

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The assistance of Drs. Norwood, Pigott and Bailey in the descriptions of the surgical techniques and of Drs. Norwood, Weinberg, Clark, and Chin in reviewing the manuscript is gratefully acknowledged.

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CHAPTER 79

Aortic Stenosis: Valvular, Supravalvular, and Fibromuscular Subvalvular

Larry A Latson

Aortic stenosis is a term commonly used to describe any of several distinct lesions that cause obstruction to left ventricular outflow by an anatomic abnormality in proximity to the aortic valve. Detailed autopsy studies have shown that abnormalities of the aortic valve are probably the commonest of the congenital heart defects and may be seen in approximately 1% of the general population.[1] However, these bicuspid valves function well throughout childhood and often go undetected for many years. Thus, patients with such mildly deformed valves are not included in most clinical series on pediatric aortic stenosis. Children with bicuspid aortic valves should be detected as early as possible, however—even if the valves are functioning normally. There is a significant risk of bacterial endocarditis in these patients; they need appropriate counseling concerning antibiotic prophylaxis. In addition, we evaluate these patients clinically every 2 to 3 years since as many as 70% may develop some degree of either stenosis or insufficiency by age 30.[1,2] Calcification of these valves occurs commonly (but not invariably) after the third or fourth decade.

In this chapter, we will deal with the so-called fixed forms of aortic stenosis: aortic valvular stenosis, fibromuscular subvalvular aortic stenosis, and supravalvular aortic stenosis. As a group, these lesions usually are listed as the fourth or fifth most common form of congenital heart disease, occurring in 3 to 8% of patients with congenital cardiac malformations.[3-5] Although the physical findings and pathophysiologic effects of these lesions are similar enough that they are often grouped together, the epidemiology, natural history, and treatment varies significantly. Therefore, we will discuss each of these lesions separately.

AORTIC VALVULAR STENOSIS

Aortic valvular stenosis is the most frequent cause of "fixed" aortic stenosis; it occurs in 60 to 75% of patients with aortic stenosis in most series.[4,6,7] There is a definite sexual predilection, with aortic valve stenosis affecting males three to five times as often as females.[7-9] Associated congenital cardiac defects are seen in up to 20% of patients who have aortic valve stenosis as their major hemodynamic abnormality. The most commonly associated malformations are patent ductus arteriosus, coarctation of the aorta, and ventricular septal defect.[4,10]

Early descriptions of patients with aortic valve stenosis date as far back as the 1600s.[11] Prior to the early 1900s, most of the recognized cases of aortic valve stenosis were autopsy descriptions of calcific aortic stenosis in adults or critical aortic stenosis in young infants. It was not well appreciated until the early 1900s that the abnormal aortic valves seen in many older pediatric and young adult patients dying with calcific aortic stenosis were congenitally malformed.[11] It was, however, clearly recognized much before that time that aortic stenosis was a serious condition that often resulted in sudden death.[7,11,12]

Natural History of Untreated Forms

The "natural" history of patients with aortic valve stenosis is complex to ascertain because accurate diagnostic and surgical treatment techniques evolved at similar times.[7] Prior to the 1950s, the clinical diagnosis of aortic stenosis was uncertain (except in the most classic cases) and the degree of severity was difficult to assess. As better techniques for diagnosis and assessment of severity developed, patients with suspected severe stenosis often

were sent for surgical intervention and thus were not available for long-term follow-up of the "natural" history. The best possibility for studies on this subject are probably those involving patients diagnosed in the 1950s.[7,8,11]

Pediatric patients with aortic valve stenosis can be considered in two groups: 1) those with stenosis severe enough to lead to symptoms or definite diagnosis in infancy (usually prior to 1 year of age) and 2) those patients who are not initially diagnosed until at least 2 years of age. Approximately 10 to 15% of patients with aortic valve stenosis fall into the infantile group.[4,13,14] These patients usually have a more severe form of stenosis. Campbell estimated that 23% of patients with infantile aortic valve stenosis died in infancy when surgical intervention was unavailable.[7] In contrast, patients who survived the first year of life had a mortality rate of only 1.2% per year for the next two decades. Overall, the mean age of death in patients with valvular aortic stenosis was estimated to be 35 years with approximately 20% of patients dying in the first two decades of life. Although 60% of patients were alive at 30 years of age, 60% had died by 40 years of age. Many patients succumbed to progressive congestive heart failure, but over half died suddenly and unexpectedly.[7,11] The incidence of bacterial endocarditis was approximately 1% per year.

Anatomy and Embryology

The normal aortic valve is composed of three pocket-like cusps of approximately equal size with a semilunar shape to the free margins of the cusps. The cusps are normally smooth and pliable with a fibrous nodule—the nodulus Arantii—at the center of the free margin of each cusp.

In the embryo, the aortic valve is formed from three thick tubercles: two on the distal edge of the truncus swellings that septate the primitive truncus and a third from an intercalated valve swelling that appears opposite the two truncus swellings.[15] By the process of excavation, the swellings are transformed into the thin cusps of the valve and the sinuses of Valsalva. Formation of the aortic valve is virtually complete by 60 days of gestation.

The most frequent malformation of the aortic valve is the presence of only two cusps: the bicuspid aortic valve. In most cases, the leaflets of the bicuspid aortic valve are of unequal size and a raphe or false commissure is seen in one of the leaflets.[1,12] When the cusps are oriented toward the right and left, the raphe will usually be in the right cusp with the coronary arteries arising from behind each cusp. When the cusps are situated anteriorly and posteriorly, the raphe is usually in the anterior cusp, and both coronary arteries arise in front of the anterior cusp.[6] Because the free margins of a bicuspid valve are relatively straight rather than semicircular, mobility is limited. Although the majority of bicuspid aortic valves create minimal stenosis or no stenosis, thickening of the leaflets and partial fusion of the two leaflets can lead to severe stenosis even in the pediatric age group (Fig. 79–1).

Fusion of all three leaflets of the aortic valve leads to a unicuspid valve. This type of valve may have a central opening (with no true commissure) or may have a small eccentric slit-like opening extending to the annulus (making it unicommissural) (Fig. 79–1). In general, the fewer the number of cusps and commissures, the greater the likelihood that the valve is stenotic at birth.[6]

Uncommon causes of aortic stenosis at the valve level include myxoid dysplasia and annular hypoplasia. Valves with myxoid dysplasia may be tricuspid, but obstructive, because of the sheer bulk of the cusps. Myxoid dysplasia appears to be due to failure of transformation of embryonic myxoid tissue into the normal dense connective tissue of the valve.[16,17] In the rare patient with isolated hypoplasia of the aortic annulus, the aortic valve is usually only slightly abnormal.[6,18]

The left ventricle often shows secondary changes in infants with critical aortic stenosis. Mitral insufficiency is commonly found in association with pathologic evidence of papillary muscle infarction and fibrosis.[13,19] Endocardial fibroelastosis is seen in over 50% of infants who come to autopsy.[19,20] Left ventricular size can be increased or decreased.[21,22]

Etiology

The etiology of aortic valve stenosis is unknown. The pattern of occurrence in most families appears to be multifactorial. Recent

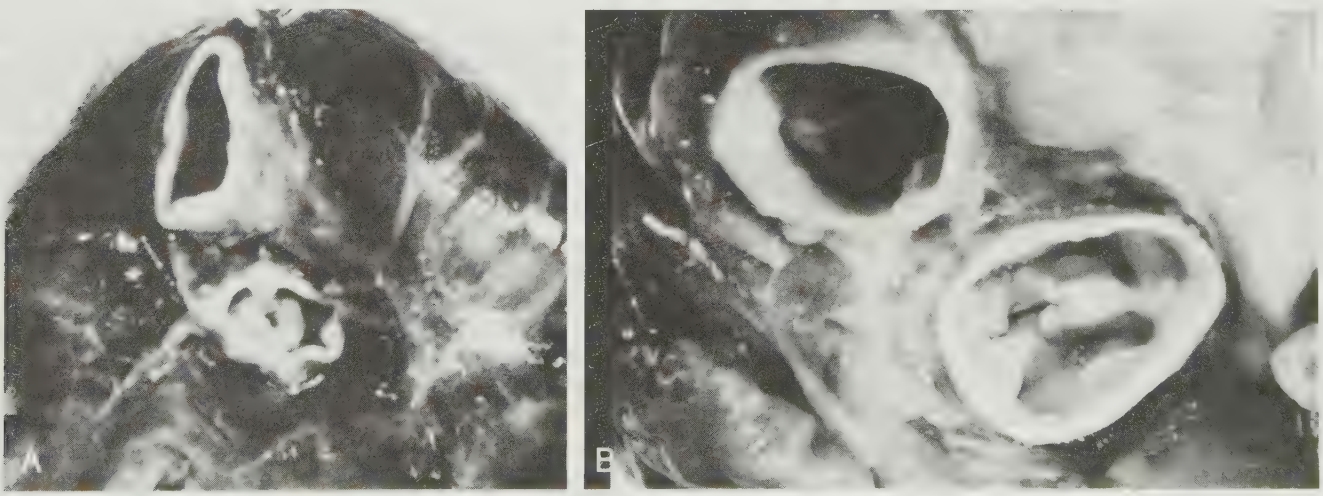

Fig. 79–1. Morphology of aortic valvular stenosis. (A) A unicuspid valve from a neonate with critical aortic stenosis is shown in the left panel. The aortic valve is markedly thickened, and there is only a small central orifice. The patient died suddenly 12 hours after apparently successful valvotomy. (B) Bicuspid aortic valve from a teenager is shown in the right panel. The leaflets are fused at the superior margins. Despite the markedly abnormal appearance, the valve was only mildly stenotic, and the patient died of unrelated causes.

studies have shown that the recurrence risk in the offspring of an affected father is only 3% whereas if the mother is affected, the recurrence risk is 13 to 18%. Mitochondrial cytopathy, vertical transmission of a slow virus, or other cytoplasmic (as opposed to chromosomal) abnormalities have been suggested as possible explanations for this difference.[23]

Abnormal fetal hemodynamics also may be related to the development of aortic valve stenosis and associated abnormalities. Premature closure of the foramen ovale has been associated with left heart hypoplasia.[24,25] Experimental interference with flow through the left AV valve in the chick embryo leads to varying degrees of left heart hypoplasia and aortic valve abnormalities.[26] Experimental obstruction to left ventricular outflow can induce hypoplasia of the left ventricle,[27] an associated finding in many patients who die of critical aortic stenosis in infancy.[20,21]

Physiology

Intrauterine adaptations of the circulation to even severe valvular aortic stenosis appear adequate to maintain normal growth and development of the fetus. In patients with critical stenosis, the fetal circulatory pattern is undoubtedly much like that in patients with hypoplastic left heart syndrome: The right ventricle supplies an increased proportion of systemic blood flow via the ductus arteriosus and left ventricular output is reduced. After birth, reduced pulmonary vascular resistance results in an increased volume of blood being delivered to the left ventricle. If the left ventricle is unable to fill and eject a normal volume of blood and the ductus constricts, systemic cardiac output no longer can be supported. Thus, patients with critical aortic stenosis who are dependent upon ductus flow may present abruptly with hypotension and shock at several days to weeks after birth when the ductus constricts. Infants who can maintain a reasonably normal cardiac output after ductal closure may have no symptoms or milder symptoms of congestive heart failure without circulatory collapse.

In all but the most severe forms of aortic stenosis, the resting cardiac output, heart rate, and mean systemic arterial pressure are normal.[28,29] To maintain this normal flow and systemic arterial pressure, left ventricular systolic pressure and, consequently, total work are elevated.[30] The increased systolic work in mature subjects results in hypertrophy sufficient to maintain wall stress at near normal levels.[31,32] In immature subjects, hyperplasia as well as hypertrophy may occur. Hyperplasia may explain why patients with congenital aortic stenosis show thickening of the left ventricle even as older children and adults.[33] The contractile state of the left ventricular myocardium in asymptomatic patients with aortic stenosis appears normal.[29,34]

A relative reduction in coronary blood supply to the hypertrophic left ventricle is one of the major hemodynamic derangements of severe aortic valvular stenosis. Subendocardial ischemia and infarction can be seen in patients with patent coronary arteries. Subendocardial coronary blood flow occurs predominantly in diastole. An estimate of the potential flow can be obtained by planimetry of the area between aortic and left ventricular pressure tracings from the dicrotic notch to the onset of ventricular systole. This area has been referred to as the diastolic pressure time index (DPTI).[35,36] Similarly, left ventricular oxygen requirement can be estimated by a systolic pressure time index (SPTI) defined as the area under the left ventricular pressure curve from the onset of systole to the dicrotic notch. The ratio of DPTI:SPTI has been used as an estimate of the supply:demand ratio of the left ventricle. This ratio (or variations of this ratio) has been useful in explaining ECG changes in some patients who apparently had less severe stenosis by other estimates of severity.[36,37] Coronary stenosis or obstruction can result in less coronary flow than would be predicted from the DPTI. Ischemic changes without a markedly abnormal DPTI:SPTI ratio should suggest this problem.[38] In patients without coronary disease, the major deficit of myocardial oxygen supply occurs in the subendocardial layers. This explains the pattern of distribution of primarily endocardial fibrosis in the left ventricle in infants dying with aortic stenosis.[37,39]

The demands of exercise present significant problems to patients with aortic valve stenosis. In order to increase cardiac output, there is usually a relatively large increase in heart rate and a variable increase or even decrease in stroke volume.[28,30] Standard hydraulic formulas indicate that the mean gradient across a stenotic valve is proportional to the square of the flow rate with each systole. Although stroke index increases only slightly, heart rate nearly doubles with maximal supine exercise. The tachycardia results in shortening of both the systolic ejection period and diastolic filling time.[40] The decreased systolic ejection period results in a faster ejection rate. Thus the peak systolic gradient increases (to a variable degree) with exercise in pediatric patients.[28] Diastolic filling period, the time during which flow occurs in the coronary arteries, is shortened even more than the systolic ejection period. Therefore, exercise-induced tachycardia in patients with severe valvular aortic stenosis results in decreased myocardial oxygen delivery at a time when systolic work is increased dramatically.[36]

The presence of baroreceptors in the left ventricle in dogs has been described.[41] Sudden increases in left ventricular pressure result in reflex vasodilation, primarily in the vascular bed of skeletal muscle. Although these baroreceptors are less well described in humans, it has been postulated that sudden activation of such baroreceptors by abrupt increases in left ventricular pressure in patients with aortic stenosis could lead to a fall in systemic arterial pressure with consequent reduction in coronary blood flow. This may be one mechanism for sudden death in aortic stenosis.[42]

Clinical Features

The majority of patients with congenital aortic stenosis are relatively asymptomatic in childhood, but approximately 10% present with signs and symptoms of congestive heart failure within the first year of life.[14] Symptoms are unusual in the first days of life. Two-thirds of patients with infantile aortic valvular stenosis develop symptoms by 2 months of age. A small number of these cases develop symptoms after 6 months of age.[13,14,43–45] Tachypnea, poor feeding, and growth failure may be prominent in infants with congestive heart failure. Hepatomegaly and peripheral edema may be evident. Patients presenting at less than 1 month of age present in a shock-like state with poor peripheral perfusion and frank cyanosis, similar to patients with the hypoplastic left heart syndrome.

In young infants, the most prominent physical findings with critical aortic stenosis may be a hyperactive precordium and poor pulses. In patients under 2 years of age, the precordial impulse often suggests right ventricular hyperactivity. Most infants with severe valvular aortic stenosis have at least a soft ejection murmur along the upper left sternal border radiating to the neck. The murmur may be very inconspicuous in younger patients with severe

failure. The typical murmur of aortic stenosis is present in fewer than 20% of young infants.[13] An ejection click is often intermittent and may depend on the hemodynamic status of the patient. A prominent gallop rhythm is present in about one-half of the infants with critical aortic stenosis.

In striking contrast to patients with infantile aortic stenosis, older pediatric patients with valvular aortic stenosis are nearly always asymptomatic. Normal growth and development are found in at least 95% of these patients.[46,47] The most common symptom, when any symptom occurs, is easy fatigability. This is a relatively subjective symptom and has been reported in 15% of patients with gradients under 25 mm Hg, whereas over two-thirds of patients with severe aortic stenosis do not have this symptom.[48] Anginal chest pain and syncope are much more specific and worrisome symptoms, but they occur in fewer than 5% of all pediatric patients with aortic valve stenosis. In the Joint Study on the Natural History of Congenital Heart Defects,[48,49] angina did not occur in patients with a gradient less than 25 mm Hg. Angina showed a trend toward increasing incidence (up to 9%) in patients with moderate to severe stenosis. Syncope occurred in less than 5% of patients with gradients under 80 mm Hg and in 9% of patients with gradients over 80 mm Hg. Subjective symptoms alone do not discriminate between mild and severe aortic valve stenosis, but a history of syncope or probable angina demands further evaluation.

The physical findings of aortic valve stenosis in older pediatric patients are characteristic enough that the diagnosis generally can be made on the basis of physical examination. Vital signs, including blood pressure, are normal in all but the most severe cases.[48] Although the shape of the chest is generally normal with no evidence of a precordial bulge, inspection and palpation may provide some clues to the diagnosis. A sustained, visible apical impulse with a presystolic motion indicates left ventricular hypertrophy with prolonged ejection in patients with severe stenosis. The heart is usually normal in size to palpation, but increasing severity leds to an increase in the force of the normal left ventricular impulse. Severe hypertrophy generally is accompanied by a strong and sustained heaving movement of the apex that may be accompanied by a presystolic tap implying an increased force of left atrial contraction in a patient with elevated end-diastolic pressure.[50] A systolic thrill is palpable in up to 85% of patients with even mild aortic stenosis. The thrill is maximal at the upper right or upper left sternal borders radiating cephalad and to the right into the carotid arteries.[48,50] The presence of a precordial (at the lower sternum or apex) thrill by definition indicates a murmur of at least grade IV intensity. Suprasternal notch thrills, however, are common in patients who may have precordial murmurs of only grade II or III intensity.

The murmur of aortic valvular stenosis is a classic "systolic ejection" (systolic crescendo-decrescendo) murmur beginning shortly after the first heart sound or immediately after an ejection click, if one is present. The murmur radiates along the course of the ascending aorta and is usually loudest where the aorta is closest to the precordium (at the right upper sternal border in older children and closer to the left upper sternal border in toddlers). The first heart sound generally is normal but must be distinguished from the ejection click that is present in 60 to 90% of children with valvular aortic stenosis.[10,46,47] The ejection click occurs after the first heart sound and is usually loudest at the left lower sternal border or at the apex. Unlike a pulmonary ejection click, the timing and intensity do not vary with respirations. A soft, low-pitched, and short ejection murmur preceded by a relatively late ejection click is typical of mild aortic stenosis. Increasing degrees of stenosis are accompanied by a louder, higher-pitched, and longer murmur that peaks later in systole. The ejection click occurs closer to the first heart sound with more severe stenosis and may not be audible in patients with critical obstruction.

In mild aortic stenosis, the second heart sound normally is split. With increasing severity of stenosis, left ventricular ejection is prolonged so that the normal widening of the second heart sound with inspiration is diminished. In severe cases, there may be paradoxical splitting of the second heart sound, but more than 80% of patients with severe aortic stenosis still have normal variation of the second heart sound with inspiration.[48] An early diastolic murmur of aortic insufficiency is noted in 15 to 25% of pediatric patients with aortic stenosis.[10,51] This murmur usually is more pronounced in patients with mild or moderate degrees of stenosis. A definite fourth heart sound, which may be accompanied by a presystolic tap, usually indicates significant left ventricular hypertrophy with elevation of left ventricular end-diastolic pressure.

Noninvasive Evaluations

Electrocardiogram

The resting electrocardiogram in infants with critical aortic stenosis is seldom normal, but seldom diagnostic. The frontal plane QRS axis is within normal limits in at least 75% of cases, but both left axis deviation and right axis deviation are seen.[13,14] Right ventricular hypertrophy is the predominant pattern in infants under 1 month of age.[44] Left ventricular hypertrophy is reported in more than three-fourths of older infants.[13,14,43] Inverted T waves and/or ST depression in the left precordial leads (strain pattern) is seen in up to 90% of young infants with critical aortic stenosis.[13,43] Both right and left atrial enlargement are found occasionally as is first degree atrioventricular block. Arrhythmias and more advanced atrioventricular conduction defects are rare.[14] In nearly all series of infantile aortic stenosis, at least one patient wtih severe stenosis and a normal electrocardiogram is reported.[52] In patients under 2 years of age, neither the presence of left ventricular hypertrophy nor the presence of T-wave abnormalities has proven sensitive enough to estimate the degree of severity.[49]

In pediatric patients over 2 years of age, the resting electrocardiogram is only moderately useful in distinguishing the degree of severity of aortic valvular stenosis. The QRS axis is normal in more than 90% of patients.[49] Left ventricular hypertrophy, defined as abnormally high amplitude in V6 (greater than 30 mm or greater than two standard deviations above the mean for age), is more common in patients with more severe stenosis (40% of patients with a gradient less than 25 mm Hg versus 68% of patients with gradients greater than 80 mm Hg).[49] Presence of an S wave greater than 30 mm in lead V1, a very small or absent Q-wave in lead V6, and T-wave inversion in lead AVF all suggest more severe stenosis.[49,53] The most discriminating electrocardiographic parameter may be the T wave in lead V6. The T wave is upright in over 90% of patients with mild or moderate stenosis, but flattened, biphasic, or inverted in 50% of patients with a gradient greater than 80 mm Hg.[49] Serial ECGs showing increasing left ventricular voltage with the development of ST and T wave changes, even

without the development of definite left ventricular hypertrophy may suggest increasing stenosis.[9]

Exercise Test

In patients old enough to cooperate, an exercise electrocardiogram may improve the sensitivity for detecting patients with severe stenosis. Most authors consider the development of ST depression of more than 1 mm persisting longer than 0.08 seconds after the J point to be indicative of possible ischemia.[40] Early reports indicated that a positive treadmill test was highly sensitive and specific for a gradient greater than 50 mm Hg.[54] Later reports, however, found that there is a relatively high false positive rate of up to 40% in patients with a gradient less than 50 mm Hg.[55–57] Some patients with a positive test but low gradient have elevated end diastolic pressure.[58] The test appears to be less useful in postoperative patients.[58]

Maximal exercise capacity is seldom reduced in patients with aortic stenosis.[55,59] An increase in systolic blood pressure greater than 35 mm Hg with exercise is seldom seen in patients with severe stenosis but, unfortunately, many patients with mild stenosis also do not increase their blood pressure by more than 35 mm Hg.[55,57]

Chest Roentgenogram

Patients with infantile aortic stenosis who are symptomatic show generalized cardiomegaly in almost all cases. This enlargement may be severe, particularly in patients under 1 month of age.[13,14,44] Normal heart size has been reported in fewer than 15% of cases.[43,49] Pulmonary vascular markings usually are considered normal but some congestion is reported in 30 to 50%. The ascending aorta is usually not visible in young patients so that dilation of the ascending aorta is seen rarely.[14]

In older patients, roentgenographic findings of cardiac enlargement are present in fewer than 10% of patients with gradients under 65 mm Hg.[9,48] More subtle findings of rounding of the left ventricular apex and posterior displacement of the left ventricular silhouette may be seen in 25% of patients.[46] Although the incidence of cardiomegaly may approach 25% in patients with gradients over 80 mm Hg,[48] there is little correlation between the degree of cardiac enlargement and severity of stenosis.[10] The presence of definite cardiomegaly in an older pediatric patient with aortic valve stenosis suggests either left ventricular failure or the development of significant aortic insufficiency and is associated with a poor immediate prognosis.[60] Dilation of the ascending aorta develops with age. Aortic dilation is seldom seen in patients under 6 years old but is present in 40 to 60% of older patients.[9,10]

Echocardiography

Aortic valvular stenosis was one of the early congenital cardiac lesions identified by m-mode echocardiography. The m-mode features of aortic valve stenosis include multiple diastolic echoes of the aortic valve (instead of the normal single closure line) and apparent asymmetric opening and closure of the valve.[61,62,63] Because the m-mode echocardiogram can be altered markedly by transducer position and angle, two-dimensional echocardiography is superior for evaluating the morphology of the valve.[64] M-mode echocardiography, however, does provide a simple method to measure left ventricular size, wall thickness, and estimate ventricular function. Early studies showed weak correlation of left ventricular shortening fraction, abnormal left ventricular wall motion, or systolic time intervals to severity of aortic valve stenosis.[65–67] Left ventricular peak systolic pressure can be estimated from the m-mode echocardiographic measurements of left ventricular posterior wall thickness in systole (LVPWs) and left ventricular cavity dimension in systole (LVs). Based on the concept that sufficient hypertrophy occurs to maintain normal left ventricular wall stress, the left ventricular systolic pressure (LVPs) is estimated from the formula $LVPs = 225 \times (LVPWs/LVs)$.[68] The aortic valve gradient can be estimated by subtracting the arm blood pressure from LVPs. Unfortunately, this measurement is not reliable in patients with aortic insufficiency. Individual measurements may underestimate or overestimate left ventricular pressure by 20 mm Hg.[68,69]

Two-dimensional echocardiography offers improved evaluation of the morphology of the aortic valve. In the long axis view, the valve usually appears thickened. The symmetry of opening and closing can be evaluated. In diastole, the leaflets often can be seen to prolapse.[70] In systole, the leaflet motion appears restricted and the leaflets often appear to "dome."[64] The aortic valve appears thickened in the short axis view, and the location of the aortic commissures can be evaluated. The typical pattern in diastole is that of a single long commissure that may be either horizontal or vertical.[70] Many bicuspid aortic valves have a raphe that gives the appearance of a tricuspid valve in diastole (Fig. 79–2). Careful analysis of the echocardiogram in slow motion, however, will reveal the typical "fish mouth" appearance of the valve in systole. In some patients, the orifice of the valve can be visualized, but measurement of this orifice area has not proven accurate in determining severity of aortic valve stenosis.[71] Two-dimensional echocardiography is useful in ruling out other sites of left ventricular outflow tract obstruction such as sub- or supravalvular aortic stenosis.[72]

The presence of aortic valvular stenosis results in a high-velocity jet with turbulent blood flow beside and downstream from the jet. These disturbed flow patterns can be identified in the majority of patients by useful examination with pulsed Doppler echocardiography.[73] The presence of disturbed flow on pulsed Doppler is sensitive for identifying the presence of even mild obstruction. Measurement of the velocity of blood in a central jet by continuous wave Doppler is superior to pulsed Doppler for estimating severity of obstruction.

Continuous wave Doppler echocardiography lacks the spatial resolution of pulsed Doppler, but provides a means to measure the high systolic blood flow velocities in the central jet of patients with aortic valvular stenosis. Intuitively, ejecting a fixed amount of flow through a smaller orifice will result in an increase in the veolicty of blood as it is ejected. The instantaneous pressure gradient across a thin obstruction such as a stenotic valve can be accurately estimated from the simplified Bernoulli equation: pressure gradient $= 4 \times$ peak velocity^2 (Fig. 79–3).[74] This formula has been tested extensively in both experimental animals and in humans.[75–79] Unfortunately, this relationship relates instantaneous pressure gradient to instantaneous velocity. In clinical practice, we have traditionally estimated stenosis using the peak-to-peak pressure gradient between the left ventricle and ascending aorta. Since peak pressure in the left ventricle does not occur simultaneously with the peak pressure in the aorta, the highest instanta-

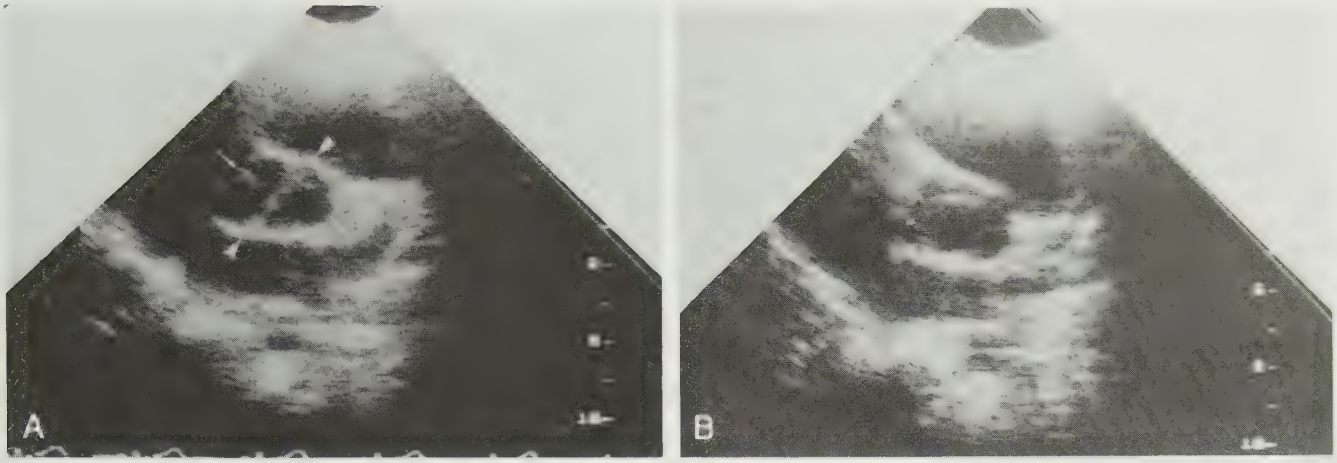

Fig. 79–2. Echocardiogram of mild aortic valvular stenosis. Parasternal short axis views of the aortic valve in diastole (A) and systole (B). The single true commissure (large arrowheads) and raphe (small arrow) are seen in the diastolic frame (A). The prominent raphe almost makes the valve appear tricuspid in diastole, but the fused right and noncoronary cusps are clearly seen as a single line in systole (arrowheads in B).

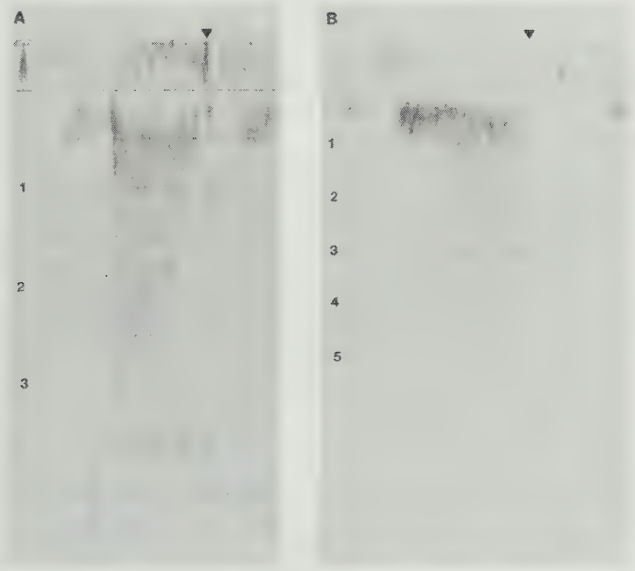

Fig. 79–3. Continuous wave Doppler in aortic valvular stenosis. Tracings from the apical window in a patient with mild stenosis (A) and severe stenosis (B). Peak velocity in (A) is 2.7 m/sec, which yields an estimated peak instantaneous gradient of $4 \times (2.7)^2 = 29$ mm Hg. The peak velocity occurs early in systole and velocity is very low immediately prior to valve closure (arrowhead). Peak velocity in (B) is 4.8 m/sec, which yields an estimated peak instantaneous gradient of $4 \times (4.8)^2 = 92$ mm Hg. The highest velocities occur later in systole than in a patient with mild stenosis, and the velocities remain high (indicating a continued gradient) very late systole.

neous gradients measured by Doppler echocardiography usually are higher than the cardiac catheterization peak-to-peak gradients (Fig. 79–4). Doppler-derived pressure gradients do not overestimate true pressure gradients, but if the maximal Doppler peak intantaneous pressure gradient is equated incorrectly with the peak-to-peak systolic gradient, overestimation is the rule.[80]

Determination of the mean pressure gradient from the Doppler signal is somewhat more tedious but correlates very well with the mean pressure gradient at catheterization.[79,81–83] Mean pressure gradients are not used commonly in pediatric cardiology but can be used to calculate valve area. This technique has proven relatively accurate in adult patients.[81,82]

Some variation between measurements performed during catheterization and nonsimultaneous echocardiographic measurements must be expected because of differences in cardiac ouput related to sedation or sympathetic tone, as well as inaccuracies introduced by the use of fluid-filled catheters.[78,84,85] Doppler tracings should be obtained from suprasternal notch, right parasternal, and apical windows in aortic stenosis patients with the highest velocities obtained for gradient calculations. Because of the importance of the Doppler gradient estimate in following patients with aortic stenosis, we do not hesitate to use sedation in uncooperative patients in order to obtain high-quality tracings.

In patients with infantile aortic stenosis, echocardiography is sufficiently sensitive and specific to eliminate the need for diagnostic cardiac catheterization in many critically ill patients.[86–88] Two-dimensional echocardiography demonstrates a thickened and abnormal appearing aortic valve with markedly reduced mobility. In symptomatic patients, the thickened leaflets are always visible in both systole and diastole (Fig. 79–5). Extremely thickened valves will show very little motion through the cardiac cycle. M-mode and two-dimensional echocardiography may be used to evaluate left ventricular size, which may be an important prognostic factor.[22] The left ventricle typically appears hypertrophic. An abnormally increased echodensity of the papillary muscles of the mitral valve is seen.[89] Right ventricular enlargement and poststenotic dilation of the ascending aorta are usual in patients with symptomatic infantile aortic valvular stenosis. A complete, sys-

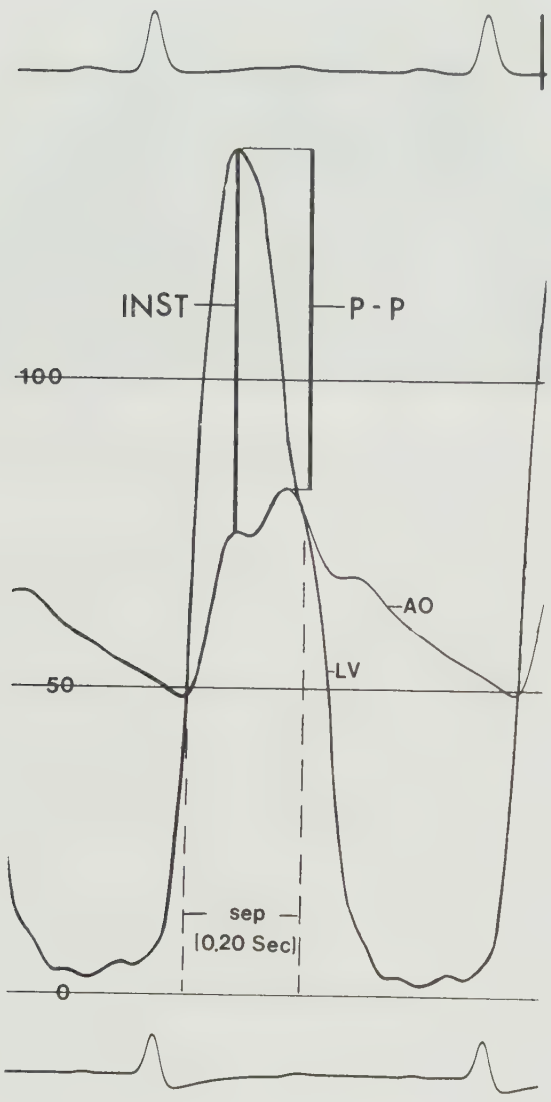

Fig. 79–4. Valve gradient and valve area from catheterization data. Simultaneous left ventricular (LV) and aortic (Ao) pressure curves in moderate aortic stenosis are shown. The peak-to-peak (P-P) pressure is the difference between the maximal LV pressure and maximal aortic pressure (54 mm Hg in this patient). Maximal instantaneous gradient (INST) is the maximal difference between aortic and let ventricular pressure at any instant in systole (62 mm Hg in this patient) and is usually slightly higher than P-P. To calculate indexed aortic valve area (AVA), one must know the amount of time during which blood is flowing through the stenotic valve (SEP) and the amount of blood flowing through the orifice—the cardiac index (CI). From the tracing above, the time of one systole (sep) is 0.2 sec and if the heart rate (HR) is 100/min, then SEP = sep × HR = 20 sec/min. The Bache formula[100] for calculation of the aortic valve area is: $AVA = Q/37.8\sqrt{(P+P) + 10}$ where Q = CI/SEP in this example, CI = 4000 ml/min/M². Therefore, $Q = 4000/(100 \times 0.2) = 200$ and $AVA = 200/(37.8\sqrt{59+10}) = 0.66$ cm²/M².

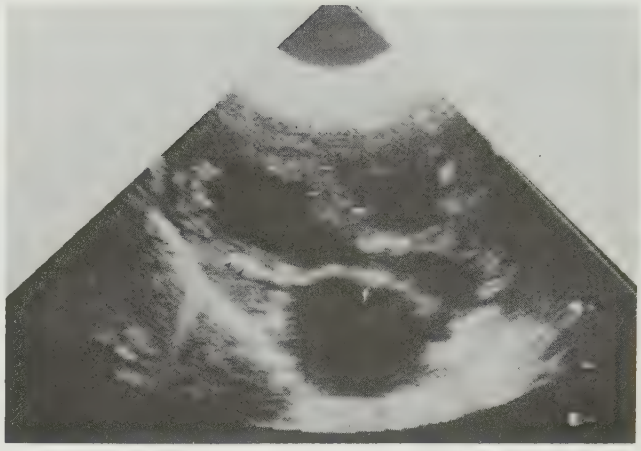

Fig. 79–5. Echocardiogram of infantile aortic stenosis. Systolic frame of parasternal long axis view of the left ventricle and proximal ascending aorta. The mitral valve is closed, and there is abnormal echodensity of the papillary muscle (black arrowheads). Persistent echoes of the aortic valve are still visible in the aortic root (white arrow). There is poststenotic dilation of the ascending aorta.

temic echocardiographic examination of the heart and great vessels is imperative to rule out associated lesions in patients who may be sent to surgery without cardiac catheterization. Pulsed Doppler echocardiography confirms the presence of disturbed flow in the ascending aorta. In patients with very poor cardiac output, the systolic flow may not suggest a high gradient (especially if much of the systemic flow is provided through a patent ductus arteriosus), but a small jet of disturbed flow should be detectable. Doppler also is useful for evaluating the presence and severity of aortic or mitral insufficiency and for identifying the presence of a patent ductus arteriosus.

Cardiac Catheterization

Although many patients with infantile aortic stenosis can be referred for surgery after complete echocardiography, cardiac catheterization is still indicated if there is any doubt about the diagnosis or if associated defects such as coarctation of the aorta cannot be completely evaluated with the noninvasive evaluations. Combined left and right heart catheterization will help evaluate the possibility of associated lesions. For diagnostic catheterization, we prefer to enter the left ventricle prograde via the foramen ovale or utilizing the Mullins long transseptal sheath technique.[90] This approach allows certain access to the left ventricle without the need to manipulate a catheter across the sometimes tiny orifice of the stenotic aortic valve. We prefer to measure the aortic valve gradient by simultaneously recording the left ventricular pressure and the ascending aortic pressure (through a small umbilical or femoral arterial catheter advanced retrograde to the ascending aorta). Femoral arterial pressure or brachial artery pressure can be substituted for the ascending aortic pressure in infants since the decision for surgery is usually not based solely on gradient measurements in this age group.

The aortic valve is best demonstrated angiographically by performing both left ventricular and aortic root angiograms.[91] We prefer the use of nonionic contrast media, particularly in patients with severe stenosis, because there is less vasodilation and less

depression in contractility. Left ventriculography is best performed with the long axial (60 degrees left anterior oblique plus 30 degrees cranial-caudal angulation) and elongated right anterior oblique (30 degrees right anterior oblique plus 30 degrees cranial-caudal angulation) projections.[92,93] These views minimize the appearance of structures overlying the left ventricular outflow tract and allow the best visualization of the subaortic and supravalvular areas. The stenotic aortic valve typically appears thickened and domes in systole.[68] There is a central jet of contrast that corresponds to the orifice of the stenotic valve (Fig. 79–6). In patients with a unicuspid valve, the jet of contrast is more likely to be directed posteriorly (in contact with the posterior wall of the aorta). In diastole, one can see a deep sinus of Valsalva anteriorly with a shallow posterior sinus in the case with a unicuspid valve.[94] The presence of extensive myocardial sinusoids suggests the presence of endocardial fibroelastosis.[21] Left ventricular volume and ejection fraction can be compared to normal values for age.[95]

Beyond the neonatal age group, cardiac catheterization for aortic valvular stenosis is performed primarily in patients with borderline criteria for surgery. Catheterization is not necessarily indicated in patients who are obvious surgical candidates based on noninvasive evaluations, and certainly catheterization is not needed in patients who have unequivocal evidence of only mild stenosis.

Hemodynamic measurements should be obtained prior to angiograms. The left ventricle can be entered using either the retrograde or transseptal approaches. If a long transseptal sheath is used to gain access to the left atrium, the left ventricle can then be entered using a straight catheter and preformed guiding wire, balloon tipped catheter, or modified pigtail catheter.[90,96,97]

Unless the transseptal catheter can be manipulated progradely across the aortic valve, measurement of the gradient requires placement of a retrograde arterial catheter in the ascending aorta. The gradient across the aortic valve should be measured by either simultaneous left ventricular and ascending aortic pressure tracings or by pullback tracing from the left ventricle to the ascending aorta. Femoral arterial pressure should not be substituted for ascending aortic pressure. In older patients with borderline gradients, pulse amplification results in higher systolic pressure in the femoral artery than in the ascending aorta and thus an underestimation of the severity of the gradient to an unpredictable degree.[98,99] In general, increasingly severe stenosis results in a more rounded or peaked appearance to the left ventricular pressure curve with an earlier and lower anacrotic notch on the aortic pressure curve. Cardiac output should be measured using either the Fick technique or an indicator dilution method. Aortic valve area can be calculated from the Gorlin formula or the simplified formula proposed by Bache (see Fig. 79–4).[30,100] The advantage of the Bache method is that planimetry is not required. The aortic valve must be indexed to body surface area in pediatric patients. The normal aortic valve area approximates 2 cm^2/M^2 body surface area; valve areas greater than 0.7 cm^2/M^2 signify mild obstruction, and valve area less than 0.5 cm^2/M^2 indicates severe obstruction. After hemodynamic measurements, left ventricular and aortic root angiograms routinely are performed to evaluate left ventricular function, ventricular hypertrophy, morphology of the aortic valve, degree of aortic insufficiency, and degree of mitral insufficiency.

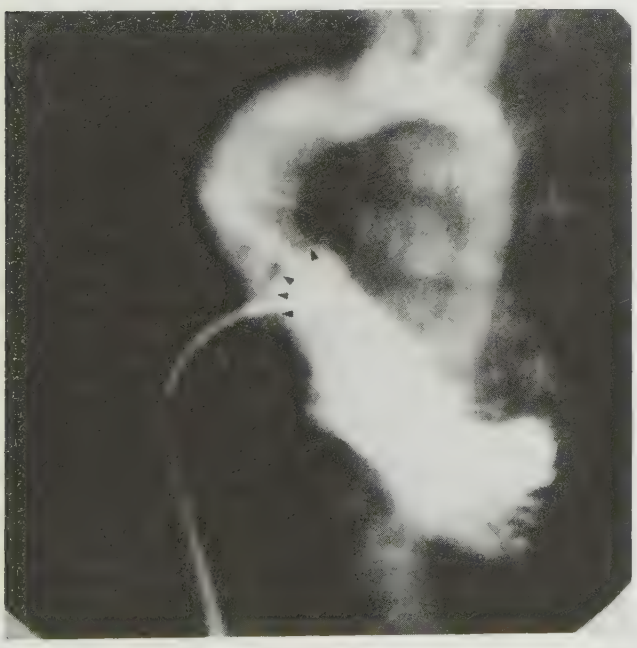

Fig. 79–6. Left ventriculogram in aortic valvular stenosis. Long axial oblique view of left ventricle in systole. The thickened aortic valve is domed (arrowheads), and a small jet of contrast is seen being ejected through the eccentric valve opening.

Treatment and Followup

Infants with aortic stenosis severe enough to cause definite symptoms of congestive heart failure are considered to have critical aortic stenosis of infancy. Such patients can deteriorate rapidly and may present a medical emergency. Those with severe heart failure and poor perfusion should be treated aggressively with inotropic support and mechanical ventilation, if necessary. In young infants, prostaglandin E_1 infusion to open the ductus may have beneficial effects,[101,102] but the potential to reduce systemic blood pressure if the ductus does not reopen should be kept in mind.[103] Following stabilization, noninvasive evaluation is obtained quickly. Echocardiographic evaluation is sufficient in many cases. If significant questions remain about the diagnosis or associated lesions, the patient is referred for diagnostic cardiac catheterization. Pressure gradient is not a reliable criterion for severity in patients with an open ductus (and right to left shunting) or low cardiac output. The presence of an angiographically abnormal aortic valve and significant symptoms is sufficient to make the diagnosis of critical aortic stenosis. Prolonged medical treatment is contraindicated because of the potential for sudden deterioration and nearly uniform failure to eliminate signs of congestive heart failure.[13,14,43] Sustained symptomatic improvement can only be expected following procedures to open the aortic valve. Surgical aortic valvotomy remains the standard approach.

Patients surviving surgery for infantile aortic stenosis often show marked clinical improvement, but there is a very high surgical mortality. Early series reported operative mortalities over 50% in symptomatic infants.[13,20] More recent reports suggest that the operative mortality has been reduced to the 25 to 50% range,[43,45,104,105] but long-term survival remains disturbingly low.[103] The high mortality may be related to associated abnormalities including mitral insufficiency with infarction of the papillary muscles,[19] small left ventricular size,[21,43] small aortic or mitral annulus,[103] or the presence of endocardial fibroelastosis.[21] Results appear to be similar whether the valvotomy is performed with inflow occlusion, total cardiopulmonary bypass, or deep hypothermia and circulatory ar-

rest. Most surgeons now prefer to perform a relatively limited valvotomy in these critically ill infants designed to produce a moderate improvement in left ventricular valve gradient without inducing severe aortic insufficiency.[104,106] This limited valvotomy may be lifesaving but should be considered palliative in some respects because of a high incidence of residual or recurrent stenosis and significant aortic insufficiency.[43,45,104]

The treatment of aortic valvular stenosis beyond the infant age group is primarily expectant. There is no question that progression in severity of aortic stenosis with age is the rule rather than the exception. Serial studies have demonstrated that the aortic valve gradient should be expected to increase in over three-fourths of patients with even mild stenosis over a 5- to 10-year period.[9,46,47] More than 50% of patients with moderate aortic stenosis at 6 to 8 years will be surgical candidates by 13 to 15 years of age. It appears that the aortic valve orifice is relatively fixed in pediatric patients and does not increase with growth.[107,108]

The most frightening complication of aortic stenosis in pediatric patients is sudden death. Among unoperated patients, aortic stenosis has been one of the most common causes of sudden death due to heart disease in pediatric patients.[109,110] Virtually all cases of sudden death attributed to aortic valvular stenosis have been associated with evidence of at least moderately severe obstruction. Many patients have had previous symptoms of angina or syncope. The majority have had left ventricular hypertrophy with strain on the ECG.[109–111] About half of the sudden deaths in aortic valvular stenosis have occurred during or immediately after exercise.[109] Prior to the widespread availability of echocardiography and treadmill exercise testing, noninvasive evaluation of the severity of aortic stenosis in pediatric patients was felt to be inaccurate enough that routine serial cardiac catheterization was recommended for all patients.[46,47]

In our practice, we do not routinely catheterize/recatheterize patients who have clear echocardiographic evidence of less than moderately severe stenosis with normal resting and exercise ECG. Exact recommendations for the classification of severity of aortic valve stenosis vary from center to center.[9,47,48,112] In our practice, we consider patients with a transvalvular gradient of less than 25 mm Hg to have trivial aortic stenosis. We do not recommend any restrictions in physical activities in these patients and generally see them for noninvasive evaluation every 1 to 2 years. We typically perform at least one echocardiographic and Doppler examination to verify the trivial nature of the lesion and repeat the echocardiographic evaluation if there are any changes in clinical or ECG indicators of severity.

Patients who have a gradient of 25 to 50 mm Hg by invasive or noninvasive studies are considered to have mild aortic stenosis. Restrictions in recreational activity are not needed in this group of patients if the treadmill test is normal.[113,114] Because of the likelihood of progression, we generally counsel parents not to encourage these children to become active in competitive athletics that require a great deal of physical conditioning. These patients are followed noninvasively every 1 to 2 years. Echocardiography is performed every one to two years and exercise stress testing is done at least once and repeated with any change in clinical or echocardiographic indicators of severity. Patients who have symptoms or definite abnormalities on the resting or exercise ECG are considered for hemodynamic evaluation. In mild aortic stenosis, the aortic valve area at catheterization should be greater than 0.7 cm^2/m^2.

Patients with a peak to peak gradient of 50 to 75 mm Hg are considered to have moderate aortic stenosis. Patients with moderate aortic stenosis are restricted from activities involving more than light exercise such as recreational swimming, bicycling, or golf.[113] Patients in this category with a normal treadmill exercise test and no symptoms are followed with yearly echocardiographic and treadmill exercise tests. Abnormalities developing in these noninvasive evaluations would be an indication for surgery without catheterization if the gradient is felt to be on the high side of this range. It must be remembered that the instantaneous gradient by Doppler echocardiography usually overestimates the peak to peak gradient (particularly if the patients are not sedated). Therefore, potential surgical candidates with an estimated gradient closer to 50 mm Hg are usually referred for cardiac catheterization. Surgery is indicated for a resting cardiac catheterization gradient over 50 mm Hg or a valve area less than 0.7 cm^2/m^2 in patients who have T-wave changes on resting or exercise ECG or who have symptoms possibly attributable to aortic stenosis. We would also consider intervention in a patient with moderate stenosis who has a very strong desire to compete in more rigorous athletics than we would allow with a gradient of 50 to 75 mm Hg.

Patients with a peak to peak gradient over 75 mm Hg have severe aortic stenosis and are considered to be surgical candidates even without symptoms and without T-wave changes. Those with clear echocardiographic evidence of severe stenosis may be referred for surgical intervention without prior cardiac catheterization. However, cardiac catheterization may be required in some of these patients who are thought to have a very high gradient predicted by echocardiography and no other indications of severity. All patients with aortic stenosis should observe SBE prophylaxis regardless of the severity of the lesion.

Surgery

The standard surgical procedure for pediatric patients (outside the infantile group) meeting criteria for intervention is an open surgical valvotomy. Valvotomy is technically possible because of the relatively pliable valve leaflets and general absence of calcification in patients under 18 years of age.[10] Aortic commissurotomy generally is performed using cardiopulmonary bypass. The commissures are incised to free the fused valve leaflets but the incision is not carried completely to the annulus.[106] Care must be taken not to incise a false commissure since this appears to produce increased aortic insufficiency.[10] Intraoperative measurement of the gradient after weaning from cardiopulmonary bypass has shown a good correlation with early postoperative cardiac catheterization.[115] Operative mortality for surgical aortic valvotomy outside the infant age group is now approximately 2%.[116–118]

Nearly all patients show a reduction in valve gradient and improvement in symptoms after surgical aortic valvotomy. However, longterm followup studies have shown that significant late problems develop in a high percentage of patients. Survival at 10 to 20 years postoperatively has been estimated at 88 and 77%, respectively.[118,119] At 10 years after surgery, 50% of patients will suffer from residual aortic stenosis with a gradient over 50 mm Hg, moderate or severe aortic insufficiency, reoperation, bacterial endocarditis, or late death.[116,118] The risk of sudden death is not completely eliminated by surgical valvotomy. However, the ma-

jority of patients who die suddenly late postoperatively have evidence of moderate or severe aortic insufficiency or residual aortic stenosis.[116,118,120] Nearly all pediatric patients with aortic valve stenosis have normal ventricular function at the time of surgery unless they have significant aortic insufficiency; poor ventricular function is generally expected to improve following relief of stenosis.[121]

Aortic insufficiency is seen in approximately two-thirds of patients following aortic valvotomy in most large series. About half of this group will have mild aortic regurgitation and in the other half the aortic regurgitation will be moderate or severe.[116,122] Patients with moderate or even severe aortic insufficiency may be asymptomatic for many years, but eventually will develop increasing left ventricular size and signs of left ventricular dysfunction. There is no indication for "prophylactic" aortic valve replacement in pediatric patients with even severe aortic insufficiency. Surgical intervention, however, must be considered in patients who develop significant left ventricular dysfunction (most easily assessed by an echocardiographic shortening fraction less than 25%), progressive left ventricular dilation (especially if the end systolic volume is greater than 60 mL/m^2), or definite symptoms of reduced exercise tolerance (best assessed by serial treadmill exercise tests).

Patients who develop recurrent stenosis may be candidates for repeat valvotomy if the initial procedure was performed in infancy. Repeat valvotomy does not appear to be beneficial in most patients who had their first operation at a later age.[123] Bacterial endocarditis remains a significant contributor to late mortality and morbidity.[108,118] Ventricular arrhythmias, may indicate a significant risk, both preoperatively and postoperatively.[124] An uncommon late complication is dissecting aneurysm of the ascending aorta caused by injury to the vessel wall from the high velocity jet of blood caused by the stenosis.[125]

Re-operation for progressive aortic insufficiency or recurrent stenosis usually entails aortic valve replacement. Although bioprosthetic valves initially seemed ideal for pediatric patients because of the reduction in need for anticoagulation, a very high incidence of valve failure was found in this age group. In some series, the incidence of tissue valve failure was as high as 8 to 20% per year. Most centers now prefer mechanical valves in nearly all pediatric patients with aortic valve stenosis.[126,127] Systemic anticoagulation with warfarin is generally recommended following placement of a mechanical prosthetic aortic valve in older pediatric patients.[128] Younger pediatric patients may be more resistant to thromboembolic events and antiplatelet agents may be sufficient, especially in children under 5 years of age who are at more risk for complications of systemic anticoagulation because of their activities.[128,129] This issue, however, remains controversial and some centers only employ antiplatelet agents in all ages.[130] Re-operation for aortic valve replacement carries a significantly higher operative mortality than the original procedure (5 to 12%), but medium-term survival is good at 86 to 94%.[118,126,129]

Patients with a small annulus either due to young age or a truly hypoplastic left ventricular outflow tract represent a special problem. Placement of a conduit from the left ventricular apex to the abdominal or thoracic aorta results in good initial relief of gradient.[131–133] However, the need for late re-operation due to conduit valve failure or progression of insufficiency of the native aortic valve has limited the utility of this procedure.[132,133] Enlargement of the aortic annulus by incision of the ventricular septum to allow placement of at least a 19 mm valve (modified Konno procedure) has proven feasible, and early results appear excellent.[134–137]

Balloon Aortic Valvotomy

Interventional cardiac catheterization procedures have developed rapidly in the last 10 years and have gained wide acceptance for some lesions. Following development of techniques for balloon valvuloplasty of pulmonary stenosis and demonstration of its safety and effectiveness, balloon valvuloplasty of aortic valvular stenosis was reported in 1983.[138,139] Since then, a number of series have been published on the use of this technique in pediatric patients.[28,140–142] In general, early results from this procedure have shown results similar to those of surgical valvotomy with approximately a 50% reduction in gradient in most patients and resulting gradients of less than 50 mm Hg in approximately 90% of patients. Development of new or slightly increased aortic regurgitation is common (as it is with surgical aortic valvotomy). Development of early postprocedure aortic insufficiency of moderate or severe degree appears to occur in approximately 10% of patients using current techniques.[142,143] Long-term results of this procedure are not yet available. The techniques for performing this procedure are still developing.[142,144,145] There are reports of mortality associated with this procedure,[144,146] but early results from the Valvuloplasty and Angioplasty of Congenital Anomalies Registry suggest that mortality is less than or equal to that of surgical valvotomy (unpublished data). Minor complications from the procedure have occurred in up to 27% of patients.[143] The most frequent complication has been transient pulse loss in the leg where the arterial balloon catheter is introduced. It is currently unclear whether the use of two smaller balloons will prove superior to the use of a single large balloon in avoiding this or other complications. Because of the relatively small number of procedures done to date and the lack of long-term followup, this procedure is still considered experimental in most centers, but holds a promise as an alternative to surgical valvotomy to palliate young patients and hopefully delay the need for aortic valve replacement.

SUPRAVALVULAR AORTIC STENOSIS

Supravalvular aortic stenosis is the least common of the three types of fixed aortic stenosis. The pathologic anatomy was first described by Cheevers in 1842.[147] In 1961, Williams reported a series of four patients who had supravalvular aortic stenosis, mental retardation, and unusual facial features.[148] In larger series, it appears that 28 to 50% of patients with supravalvular aortic stenosis have the Williams syndrome, approximately 20% have a familial form of supravalvular aortic stenosis without the other characteristics of Williams syndrome, and approximately 50% have a sporadic form of the defect.[147,149,150] Excessive vitamin D in the pregnant rabbit results in offspring that have craniofacial abnormalities and supravalvular aortic stenosis.[151] However, in humans, it is unusual to find either a history of excessive vitamin D intake during pregnancy or infantile hypercalcemia in affected patients.[152,153] In most series, males and females are approximately equally affected.

Anatomy and Embryology

Three morphologic forms of supravalvular aortic stenosis are usually reported. Fifty to 75% of patients have an "hourglass"

deformity with a constricting ridge at the superior margin of the sinuses of Valsalva.[147,149] Histologically, there is marked thickening of the media in the region of this ridge with disorientation of the medial cells as well as thickening and increased collagen content in the intima.[147,154] Approximately 25% of patients have a more diffuse type of narrowing extending for a variable distance along the ascending aorta.[149] Some series report a rare patient with a discrete membrane above the valve. This may actually be a more localized variety of the hourglass deformity.[147,155]

Although the immediate supravalvular area is the most significant area of stenosis, it is also very common for the origins of the major branches of the aortic arch to be involved.[154] Most patients also have at least minor abnormalities of the aortic valve, which is often thickened and has abnormal attachments to the supravalvular ring.[149,154] These abnormal attachments may be responsible for coronary artery stenosis.[154] Most patients with supravalvular aortic stenosis—particularly if they have Williams syndrome—also have evidence of right ventricular outflow tract obstruction that can occur at the valvular, supravalvular, or peripheral pulmonary arterial levels. The exact incidence of right ventricular outflow tract obstruction is difficult to ascertain since there is a peculiar tendency for the obstruction to improve considerably with age.[152,153]

Physiology

The major pathologic derangement in supravalvular aortic stenosis is very similar to that in aortic valvular stenosis. There is increased systolic work resulting in left ventricular hypertrophy. In most patients with supravalvular aortic stenosis, the coronary arteries are enlarged and experimental studies have shown that total mean coronary blood flow increases after supravalvular aortic constriction. However, coronary flow in diastole appears to be the major determinant of the development of ischemic changes, and diastolic flow to the coronary arteries in fact decreases significantly.[156] During exercise, the endocardial/epicardial coronary flow ratio decreases significantly in dogs with a supravalvular aortic band compared to animals with similar degrees of systolic pressure caused by renal hypertension.[157]

The systolic jet created by supravalvular aortic stenosis seems to persist along a greater distance than the jet caused by the discrete obstruction of aortic valvular stenosis. This high-velocity jet has a tendency to "hug" the wall of the aorta and transfer much of the kinetic energy into the brachio-cephalic vessels. This phenomenon, called the Coanda effect, has been demonstrated to be the explanation for the marked discrepancy in blood pressures with the right arm pressure higher than the left arm in most patients with supravalvular aortic stenosis.[158,159]

Clinical Features

Clinical features of supravalvular aortic stenosis are very similar to those of aortic valve stenosis. The majority of patients come to evaluation because of the presence of a systolic murmur. The murmur closely resembles that of aortic valvular stenosis. However, the finding of an aortic ejection click is unusual. The aortic valve closure sound may be increased.[160] Suprasternal notch thrills are very common. Because there is a high prevalence of ostial stenosis of the aortic arch vessels, discrepancies between carotid pulsations should be sought carefully. Blood pressures in both arms and in the legs should be obtained. As many as 86% of patients with supravalvular aortic stenosis will have a discrepancy in blood pressure between the arms of at least 5 to 10 mm Hg (right arm greater than left arm 80% of the time).[159]

Because individual series tend to be small, it is difficult to ascertain the incidence of symptoms. However, in most surgical series, a high portion of patients have significant disability. Dyspnea on exertion and angina are noted commonly. About two-thirds of patients have additional cardiovascular abnormalities, including pulmonary stenosis, coarctation, patent ductus arteriosus, and mitral insufficiency. When carefully sought, associated valvular and subvalvular aortic stenosis will be present in up to one-third of patients.[150] Williams syndrome is discussed in greater detail in Chapter 144. Patients with Williams syndrome have characteristic "elfin" facies, stellate iris pattern and husky voice.[161] Most of these patients are small in infancy (< 5th percentile until 3 years of age) but eventually attain normal stature.[152] Moderate to severe mental retardation is a consistent, but not universal, finding.[152] The children are often verbal and outgoing with a "cocktail personality." Most of these patients are relatively thin and have been confused with variants of Marfan's syndrome.[160]

Noninvasive Evaluations

The electrocardiogram is usually abnormal in patients with supravalvular aortic stenosis. In young patients, right ventricular hypertrophy is found commonly. In most older patients, left ventricular hypertrophy is observed, and the strain pattern is common in surgical series.[150,154] The chest x-ray is most often normal but may show mild to moderate cardiomegaly with evidence of left ventricular hypertrophy.[149,160] Dilation of the ascending aorta is distinctly absent.

Echocardiography is a valuable tool in the evaluation of patients with supravalvular aortic stenosis. The m-mode echocardiogram is useful for determining the degree of left ventricular hypertrophy. Careful "sweeps" from the left ventricle to the ascending aorta can demonstrate a narrowed area above the aortic valve with a more normal aortic dimension above the area of stenosis. However, this is a technically difficult procedure in many patients and the m-mode echocardiogram tends to underestimate the severity of the supravalvular narrowing.[162–164] More recent studies have demonstrated the utility of two-dimensional echocardiography, and this has proved to be an excellent way to demonstrate the supravalvular narrowing in our experience (Fig. 79–7).[165] Careful pulsed Doppler examination will reveal the development of turbulence and high velocity distal to the aortic valve and in the region of the supravalvular narrowing. Doppler estimates of the pressure gradient across a long supravalvular narrowing may not be as accurate as those across a more discrete narrowing such as aortic valvular stenosis.[166] Magnetic resonance imaging can also be used to demonstrate the ascending aorta and the supravalvular aortic narrowing.[167]

Cardiac Catheterization and Angiography

Because of the high incidence of associated abnormalities, it is essential that both left and right heart catheterization be performed in patients with suspected supravalvular aortic stenosis. The left ventricle can be entered using either the transseptal approach or retrograde approach. It is usually not difficult to cross the supravalvular obstruction from the retrograde approach since there is usually a funnel-shaped opening above the obstruction as well as

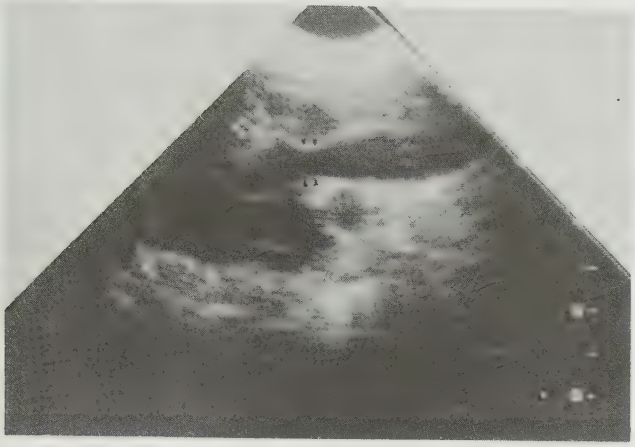

Fig. 79–7. Echocardiographic appearance of supravalvular aortic stenosis. Long axis view of ascending aorta obtained from a high parasternal window. The hourglass shape of the aorta and supravalvular narrowing (arrowheads) are visible. The aortic valve and left ventricle may be difficult to see at the same time that this portion of the aorta is well visualized.

below the obstruction. Careful pullback tracings utilizing a catheter with an endhole or closely spaced sideholes allow detection of additional gradients across the subvalvular or valvular areas. We recommend a right ventricular angiogram if there is elevation of right ventricular pressures to evaluate for peripheral pulmonary branch stenosis.[153]

A bi-plane left ventriculogram in either the AP and lateral or long axial oblique and lateral views will show the supravalvular narrowing and the ascending aorta (Fig. 79–8). Because of the high incidence of stenosis of the arch vessels, it is advisable to include these in the angiographic field.[168] An aortic root injection is also recommended to demonstrate possible coronary arterial stenosis and to detect aortic insufficiency.[149,169] Catheterization in patients with severe supravalvular aortic stenosis is not without risk, and sudden death has been described with angiography in these patients.[154]

Natural History

The natural history of supravalvular aortic stenosis without surgery is difficult to ascertain since reliable differentiation from aortic valvular stenosis was unavailable until after surgical intervention was well established. As mentioned previously, there is a high incidence of symptoms in older patients with supravalvular aortic stenosis. The few series with patients who have undergone serial cardiac catheterizations have suggested that the right ventricular obstructive lesions, which may predominate in infancy, often improve with age.[152,153] However, the supravalvular aortic stenosis tends to remain unchanged or occasionally becomes dramatically worse over a fairly short period of time.[149,150,153] Sudden death has been reported in a small number of patients.[149,154]

Treatment

Indications for surgical intervention in supravalvular aortic stenosis are similar to those in aortic valvular stenosis. Good results have been demonstrated in patients with the discrete type of supravalvular aortic stenosis. The standard approach is a lateral aortotomy into the noncoronary cusp followed by resection of the supravalvular obstruction and insertion of a dacron patch over the aortotomy.[149,150] Operative mortality is approximately 5%, and adequate reducton in gradient occurs in most patients. Small residual gradients between the aorta and left ventricle are common but may be due to coexistent valvular or subvalvular stenosis.[149] Aortic

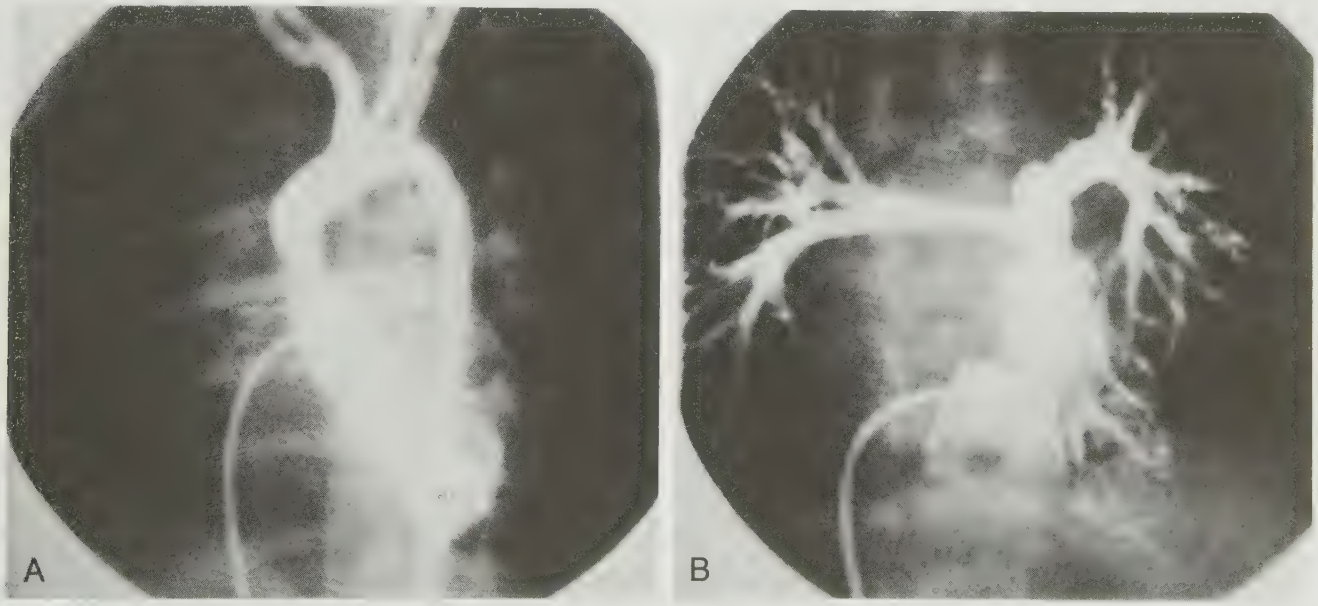

Fig. 79–8. Angiographic appearance of supravalvular aortic stenosis. (A) Long axial view of the left ventricle and aortic arch in a patient with moderate supravalvular aortic stenosis. There is a narrow segment of ascending aorta immediately above the aortic valve. The left coronary artery is dilated, and the origin of the left common carotid artery is narrowed mildly. (B) Cranially angulated view of right ventriculogram showing supravalvular narrowing of the main pulmonary artery and diffuse narrowing of the right pulmonary artery. These vessels appeared much more normal, and right ventricular pressure decreased significantly at repeat catheterization 1 year later.

valve insufficiency is present in approximately 25% of patients postoperatively. In most patients, the aortic valve continues to appear abnormal angiographically because of attachment of the aortic valve cusps to residual supravalvular tissue.[149]

The hypoplastic form of supravalvular aortic stenosis is considerably more difficult to treat surgically.[170] Particularly in earlier series, operative mortality was high and relief of gradient was less than in patients with the discrete form of supravalvular aortic stenosis. It is not clear whether more extensive aortoplasty will be completely successful in reducing the gradient in these patients.[171] Alternative procedures, including the apical left ventricle to descending aorta valved conduit, have had some success.[106,150] The majority of patients who have undergone surgery are asymptomatic. But the long-term fate of the native aortic valve, coronary vasculature, and cerebral vasculature are not known. Re-stenosis at the site of original repair does not appear to be a common problem, but the long-term fate of the distorted aortic valve is uncertain.[149] Patients who have left ventricle to aorta conduits will be at significant risk for late complications.[132,133]

FIBROMUSCULAR SUBVALVULAR AORTIC STENOSIS

Fibromuscular subvalvular aortic stenosis is the second most common form of fixed aortic stenosis, occurring in 8 to 20% of pediatric patients in most series.[171–173] As with aortic valvular stenosis, males are affected two to three times as often as females.[172,173] Unlike aortic valvular stenosis, severe subvalvular stenosis is almost never seen in newborns and only rarely in infants.[175,176] Associated cardiac malformations are more common than in patients with valvular aortic stenosis, occurring in 50 to 65% of patients.[172,177,178] The most commonly associated lesions are ventricular septal defect, coarctation of the aorta, patent ductus arteriosus, left superior vena cava, and aortic valvular stenosis.

Anatomy and Embryology

Subvalvular aortic stenosis can be caused by a thin discrete membrane, a thicker diaphragm with a muscular base (termed a collar or ridge) or a diffuse tunnel-like narrowing of the left ventricular outflow tract.[6,172,77] Seventy-five to 85% of patients have the membranous-type of obstruction. In these patients, there is a crescent-shaped, fibrous curtain attached to the ventricular septum or completely encircling the left ventricular outflow tract, located anywhere from immediately below the aortic valve to 1 cm or more into the body of the ventricle. In most series, about 10% of patients are considered to have a lesion similar to the membrane but somewhat thicker and usually associated with some protrusion of a thicker, muscular base. The distinction between this collar or ridge is often not clear-cut and not made by all authors.[172,174,177] The tunnel-type of subaortic stenosis is seen in 10 to 15% of these patients.[172,179]

There is clinical and experimental evidence that fixed subvalvular subaortic stenosis is an acquired lesion with an underlying ill-defined congenital disorder.[178] Careful study of familial subaortic stenosis in Newfoundland dogs demonstrated that subaortic stenosis develops postnatally but has a specific genetic pattern of inheritance.[180] The substrate for this postnatal development is not well understood. Rosenquist noted an increased mitral–aortic separation due to a muscular wedge in humans.[181,182] It is possible that abnormal flow patterns associated with this abnormality could lead to abnormal proliferation of tissue. Persistent embryonal endocardial cushion tissue that retrains its proliferative capacity has also been suspected.[180,183,184] Familial occurrence of subaortic stenosis in humans has been reported.[185]

Physiology

The physiology of isolated subvalvular aortic stenosis appears to be identical to that of aortic valvular stenosis. Left ventricular hypertrophy develops in response to high systolic pressures. In most patients, the degree of hypertrophy appears to be appropriate, but may be asymmetric and associated with apparent increased contractility in some patients.[6,179,186] The aortic valve frequently is thickened in patients with subvalvular aortic stenosis but is usually tricuspid. This valvular abnormality also seems to be acquired and has been ascribed to a jet lesion from the subvalvular stenosis. Trauma to the valve may be the etiology of the high incidence of aortic insufficiency seen in these patients.[6,173]

Clinical Features

The clinical findings in young patients with subvalvular aortic stenosis are frequently masked by the findings of associated lesions. A murmur is noted within the first year of life in more than one-half of patients.[172,174] Initially, it is often considered to be secondary to a small ventricular septal defect or to be functional. The murmur becomes more typical of left ventricular outflow tract obstruction as the patients become older.[172,187] Patients with isolated subvalvular stenosis have a murmur more typical for left ventricular outflow tract obstruction. There is a systolic ejection murmur maximal at the mid left sternal border with radiation to the upper sternal borders and suprasternal notch. An ejection click is heard in only 5% of patients without associated aortic valvular stenosis.[188] An early diastolic murmur of aortic insufficiency is heard in 30 to 50% of patients.[172,173,177] In older reviews, although symptoms were reported in a high percentage of cases the incidence of symptoms was undoubtedly overestimated because of the difficulty in diagnosing mild obstruction prior to the widespread use of echocardiography (i.e., there are many children with mild obstruction who are asymptomatic). In patients with mild subaortic stenosis, symptoms of chest pain and syncope are not seen.[179]

The electrocardiogram usually is abnormal in patients with subaortic stenosis. Left ventricular hypertrophy is seen in 65 to 85% of patients, but a normal ECG is seen in occasional patients with severe obstruction.[172,174] Left ventricular hypertrophy is seen in up to 50% of patients with even mild stenosis.[179] Approximately 25% of patients have a strain pattern on the ECG. Infants are more likely to show a pattern of right ventricular hypertrophy.[172,174]

Chest radiographic findings are similar to those seen in patients with aortic valvular stenosis. Heart size usually is normal but may show mild cardiomegaly or evidence of left ventricular prominence even in patients with mild stenosis. Dilation of the ascending aorta is seen in approximately 25% of patients.[174,177]

Echocardiography

The classical m-mode echocardiographic features of subvalvular aortic stenosis are seen on a sweep from the left ventricular body to the aortic root. Left ventricular hypertrophy commensurate with the left ventricular systolic pressure is seen.[186] The left ventricular outflow tract is narrowed echocardiographically in the majority of

patients; in some patients an abnormal structure in the left ventricular outflow tract can be visualized.[189–191] In addition, the aortic valve motion is abnormal with early systolic partial closure and abnormal fluttering of the valve. This abnormal fluttering and partial closure appears to be due to turbulence distal to the subvalvular obstruction.[192]

The spatial orientation provided by two-dimensional echocardiography allows clear visualization of the subaortic stenosis and differentiation of the types of aortic stenosis.[193,194] In patients with membranous subaortic stenosis, the parasternal long axis view and apical long axis view demonstrate a thin membrane below the aortic valve extending from the ventricular septum (Fig. 79–9). In some patients, a posterior attachment of the membrane can be seen along the mitral valve.[165,195,196] With the use of multiple imaging planes and newer high-resolution ultrasound equipment, most authors feel that echocardiography is superior to angiography in the recognition and characterization of subvalvular aortic stenosis.[178,195] The severity of outflow tract obstruction, however, cannot accurately be determined solely on the appearance of the subaortic area.[165,197] Pulsed Doppler echocardiography demonstrates turbulent flow below the aortic valve, and continuous wave Doppler provides a reasonably accurate estimate of the gradient across the left ventricular outflow tract.[166,197,198] Pulsed Doppler echocardiography also demonstrates the presence of aortic insufficiency.

Cardiac Catheterization

Combined left and right heart catheterization is recommended in patients with suspected subvalvular aortic stenosis because of the high incidence of associated cardiac abnormalities. The left ventricle is entered using either the retrograde or transseptal approach. Retrograde catheterization of the ventricle usually is easier than in patients with aortic valvular stenosis, but it may be quite difficult in patients with severe subvalvular stenosis.[188] Careful withdrawal of a catheter with closely spaced sampling holes often can demonstrate a pressure gradient below the aortic valve. However, a subaortic membrane is frequently close enough to the valve that this distinction is difficult or impossible. In some patients—especially those with associated ventricular septal defect—there may be little or no gradient even with definite angiographic evidence of a membrane.[187]

The left ventricular ouflow tract is best seen using the long axial projection and elongated right anterior oblique projection.[92,93] The thin membrane in the left ventricular outflow tract may be difficult to see in some phases of the cardiac cycle. Both the appearance of the membrane and the appearance of dye trapped between the membrane and the valve must be sought carefully (Fig. 79–10). The aortic valve cusps often are thickened but have a straightened (''tenting'') rather than doming appearance in systole.[169] Thirty to 50% of patients will have evidence of aortic insufficiency on aortic root injection, and the subaortic chamber may be better seen on this injection in some patients.[172] Left ventricular hypertrophy is obvious in patients with severe stenosis. Differentiation from hypertrophic cardiomyopathy is occasionally difficult; however, patients with hypertrophic cardiomyopathy usually have asymmetric septal hypertrophy and a widely patent outflow tract.[177]

Natural History

The natural history of subvalvular aortic stenosis is clouded by previous difficulty in differentiating it from aortic valvular stenosis until the widespread use of echocardiography. Much of the natural history in infants is influenced by the high percentage of patients with associated abnormalities. Congestive heart failure and sudden death are seen in some young patients but are usually secondary to associated lesions.[172]

Subvalvular aortic stenosis is a progressive lesion in the majority of patients. In recent series, up to 75% of patients have shown an increase in gradient of 25 mm Hg or more over a 5-year period.[178] This progression appears to be more rapid than in patients with aortic valvular stenosis. Rare cases with very rapid progression of stenosis are well documented.[175,178,199] This rapid progression appears to be more common in patients with the tunnel type of

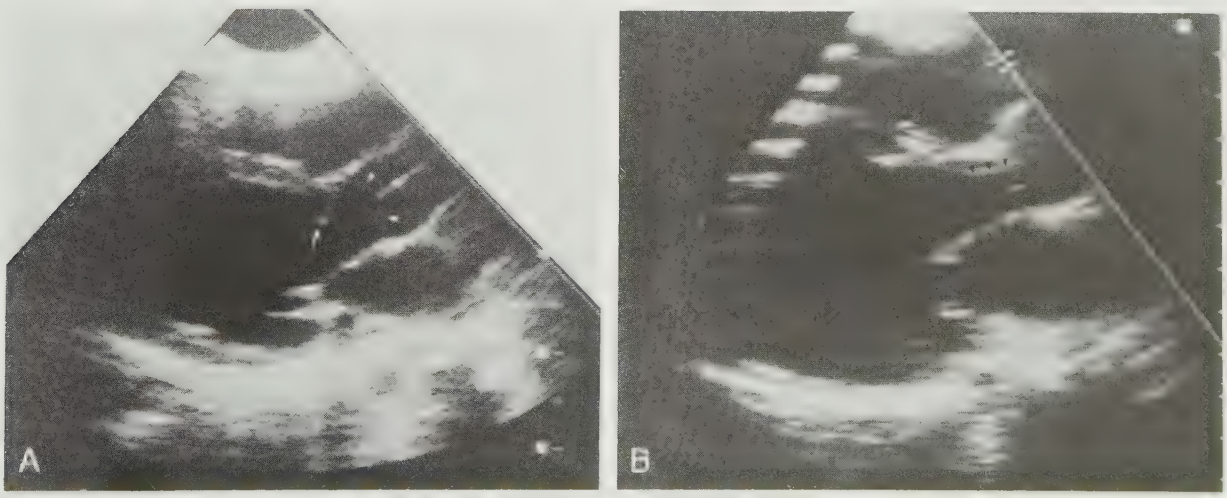

Fig. 79–9. Echocardiographic appearance of subvalvular aortic stenosis. (A) Parasternal long axis view of discrete membranous subaortic stenosis. A thin membrane (arrow) is seen extending from the septal surface of the left ventricular outflow tract immediately below the base of the aortic valve (arrowheads). (B) Parasternal long axis view of tunnel subvalvular aortic stenosis. Diffuse narrowing of left ventricular outflow tract (black arrowheads) is visible immediately below the aortic valve.

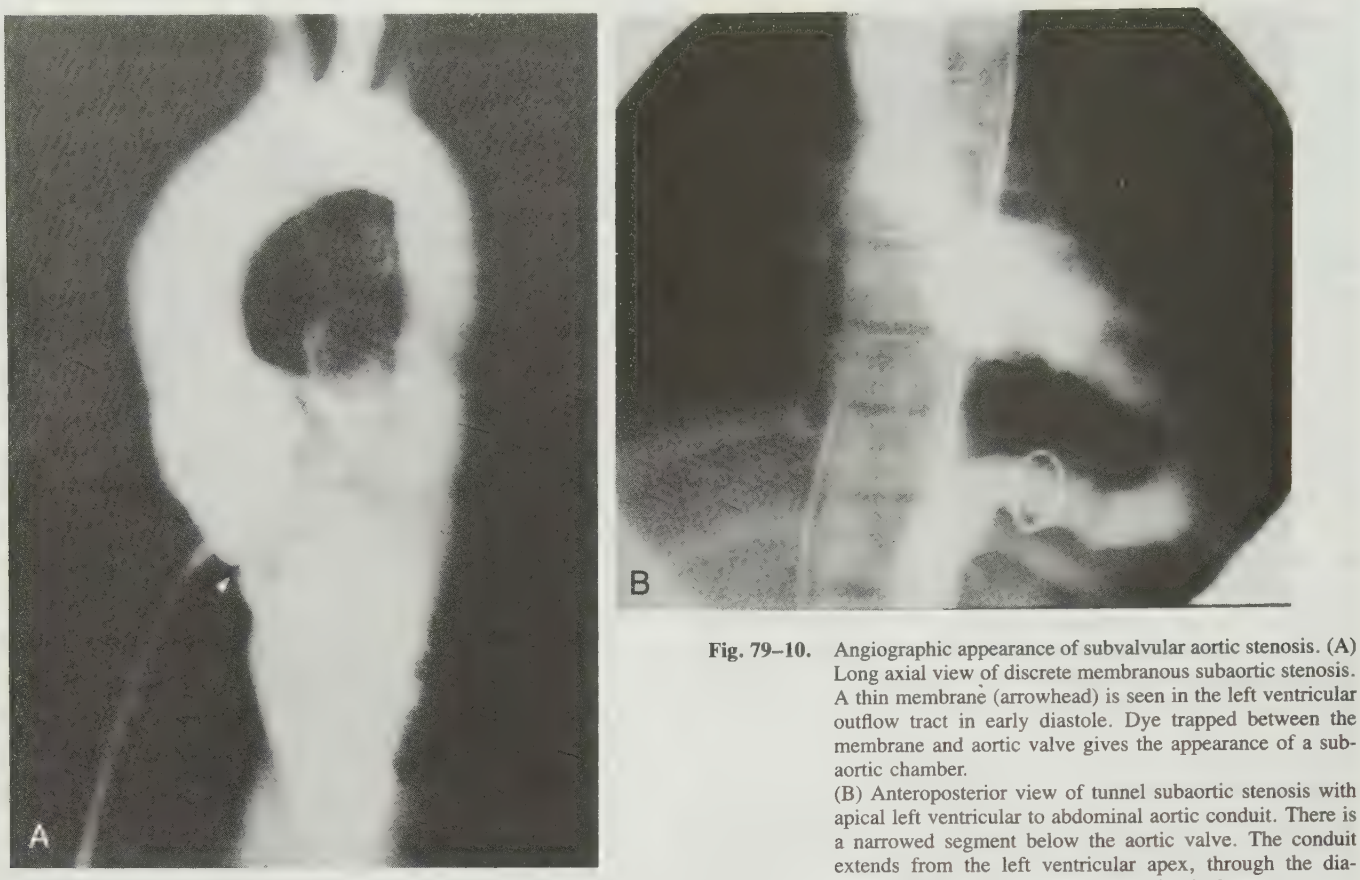

Fig. 79–10. Angiographic appearance of subvalvular aortic stenosis. (A) Long axial view of discrete membranous subaortic stenosis. A thin membrane (arrowhead) is seen in the left ventricular outflow tract in early diastole. Dye trapped between the membrane and aortic valve gives the appearance of a subaortic chamber.
(B) Anteroposterior view of tunnel subaortic stenosis with apical left ventricular to abdominal aortic conduit. There is a narrowed segment below the aortic valve. The conduit extends from the left ventricular apex, through the diaphragm, and into the supraceliac abdominal aorta.

subaortic stenosis. The incidence of aortic insufficiency also has been shown to increase with increasing age.[178,179] The degree of insufficiency is generally mild to moderate in pediatric patients unless the patient has had bacterial endocarditis.[173,177,179,200] The incidence of bacterial endocarditis may be as high as 13–25%.[183] Sudden death has been reported but the exact incidence is uncertain.[172]

Treatment and Followup

The surgical treatment of membranous subvalvular aortic stenosis is excision of the membrane under direct vision through the carefully retracted aortic valve using cardiopulmonary bypass.[106,177] It is important to remove as much of the membrane as possible without damaging the mitral valve or risking creation of a ventricular septal defect.[183] Patients with a thicker ridge or tunnel are more difficult to treat surgically. The obstruction is often well below the aortic valve and difficult to visualize. Involvement of the anterior leaflet of the mitral valve is common, and there is usually a great deal of ventricular hypertrophy.[174,177]

Resection of a subaortic membrane can be achieved with a low operative mortality ranging from 0 to 6%.[116,172,173] In the majority of patients, reduction of the gradient is good. In several series, 10 to 25% of patients have had residual gradients in excess of 50 mm Hg.[116,172,183] In some of these patients the membrane may have been incompletely excised. Some patients may, in fact, have had a more diffuse form of subaortic stenosis rather than the membranous form. In every series, the tunnel form of subaortic stenosis has a much worse prognosis. Operative mortality is higher. Simple myomectomy with attempted excision of thickened tissue results in a high percentage of patients with residual gradients.[172,174,177] Recent data indicate that subaortic stenosis may recur and require reoperation; surgery may also be necessary for treatment of increased aortic insufficiency, or for pacemaker placement in 10 to 20% of patients.[172,201] The left ventricle to aorta conduit or aortoventriculoplasty procedures are utilized in patients who require re-operation for stenosis.[106,132,133,135,137]

The major consideration in the management of patients with subvalvular aortic stenosis is to make an accurate diagnosis and determine when patients require surgical intervention. Because of the possibility of rather rapid progression, we routinely follow patients with definite subaortic obstruction every 6 months when they are less than 3 years of age and yearly thereafter. There is considerable concern generated by the likelihood of progression in this disorder. Generally, surgical intervention is considered justified with a smaller gradient than in patients with aortic valvular stenosis.[172,178] Certainly any patient requiring intracardiac surgery for an associated lesion who has echocardiographic evidence of a subaortic membrane should have the membrane excised at the same time. In most centers, a pressure gradient in excess of 40 to 50 mm Hg is also considered to be an indication for surgical

intervention.[106,179] Because surgical treatment of this lesion is by no means perfect, we do not routinely refer patients for surgery with lesser gradients. Approximately 25% of patients will show little or no progression over a long period of time without surgery. We feel that echocardiography and Doppler are sensitive for detecting any progression. Therefore, we prefer to follow our patients with lesser gradients carefully rather than routinely recommend operation. Patients who show development or progression of aortic insufficiency with even minimal gradients should be considered for surgical intervention.[178,179] Although percutaneous balloon dilation of subaortic stenosis has been reported in a small number of patients, this procedure has not yet gained wide acceptance.[202]

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CHAPTER 80

Coarctation of the Aorta and Interrupted Aortic Arch

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COARCTATION OF THE AORTA

Coarctation is a term derived from the Latin verb "arctare," meaning to make tight. It is used to describe a narrowing of the aorta most commonly occurring in the thoracic descending aorta. True coarctation results from a localized thickening of the aortic media, which protrudes into the lumen of the vessel and obstructs blood flow.

Historical milestones in the recognition of coarctation of the aorta were interestingly reviewed by Jarcho in a series of articles.[1–5] Credit for description by prosection of "narrowing of the aortic conduit" is given to Johann Meckel, whose published account in 1768 postdated by 18 years his presentation before the Royal Academy of Sciences in Berlin. The slow evolution in recognition of coarctation as a clinical entity is apparent from these readings. The anomaly, now easily characterized by physical examination, is still the subject of much investigation. This chapter will address more recent observations regarding the pathogenesis, medical, and surgical management, treatment with interventional catheterization, and long-term followup of coarctation.

DEFINITION OF TERMS

Other modifiers of coarctation are used to describe variations in anatomy, age of presentation, and pathophysiology.[6] The term "adult coarctation" (often called "postductal coarctation") has been used historically to describe a short-segment abrupt narrowing located just beyond the point of insertion of the ductus arteriosus or ligamentum arteriosum. The implication is that symptoms occur only in adults. Infantile coarctation (interchangeably called "preductal coarctation") was characterized by more diffuse narrowing of a segment of the aorta plus a constrictive zone in the isthmus beyond the origin of the left subclavian artery but proximal to the ductus arteriosus. The ductus arteriosus remains patent and inserts below the coarctation, acting as a conduit to shunt blood from the pulmonary artery into the descending aorta beyond the obstruction. Other important congenital defects of the heart are also usually present.

These classifications are limiting in that they do not allow for all the variations in anatomy and because the distinction between these types is not always clear. Isolated coarctation, or a more complicated "coarctation syndrome," can be found in patients of all ages, particularly when the natural history of the defect has been altered by surgical management.

Uniformly, coarctation of the aorta results from a peculiar ridge-like thickening of the media of the aortic wall that protrudes into the lumen of the vessel from the posterior and lateral wall; an orifice eccentric in location and displaced toward the point of insertion of the ligamentum remains (Fig. 80–1).[7] This medial thickening is typical of coarctation at any age, including infancy (Fig. 80–2). Additional thickening of the intima over the medial protuberance occurs as time elapses, and contributes to further luminal narrowing. The degree of indentation of the external surface of the aorta may be minimal in comparison to the extent of the internal narrowing. The infolding of the posterior lateral aortic wall is usually just opposite the area of insertion of the vestigial ligamentum or ductus, when patent, and is best considered to be "juxtaductal" in location (Fig. 80–3). The stricture of the aorta

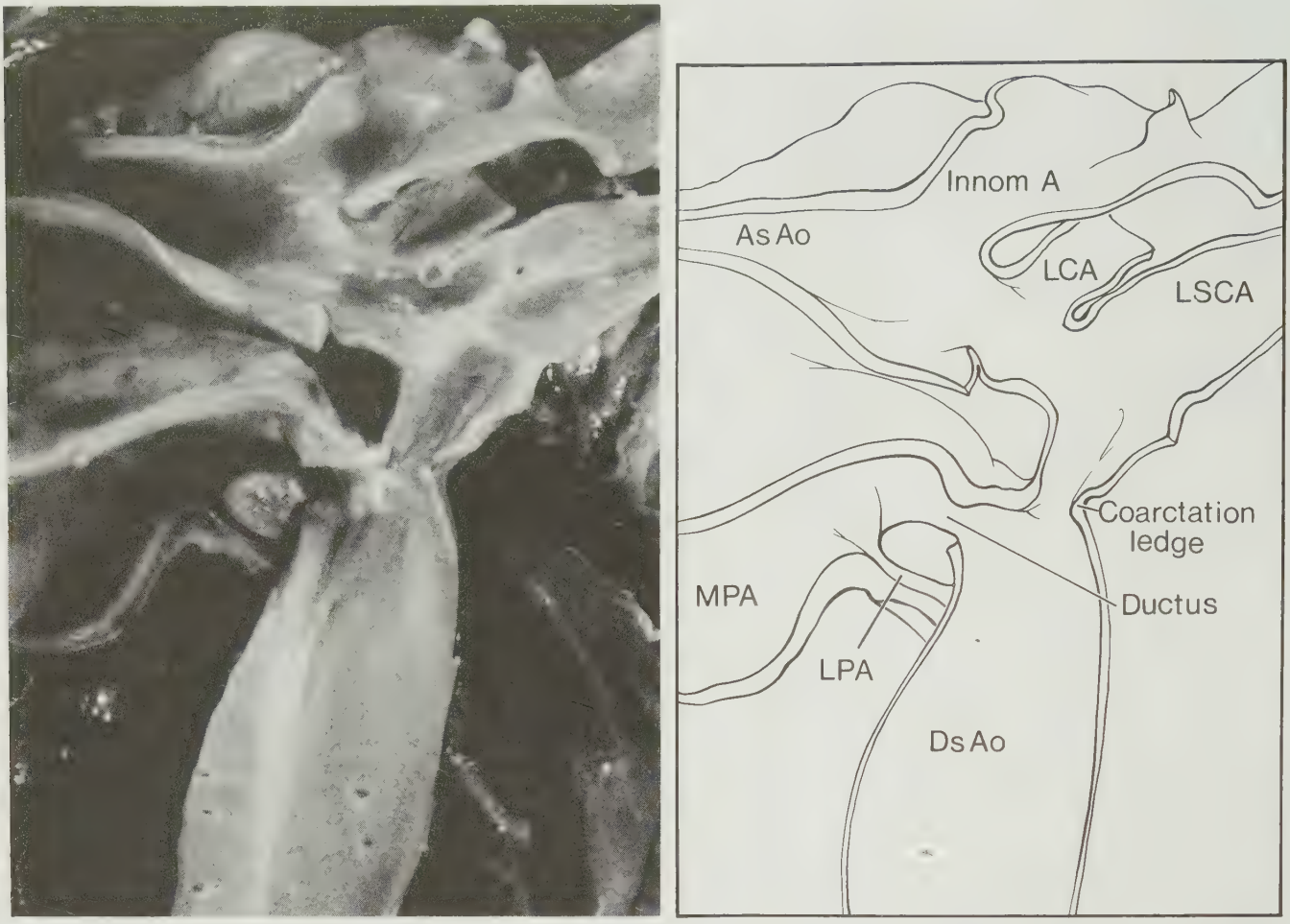

Fig. 80–1. Coarctation of the aorta; the specimen was obtained from an infant. The coarctation ledge juts into the lumen of the aorta just below the level of the left subclavian artery (LSCA). Rugations of "ductal tissue" are grossly seen on the medial wall just opposite the coarctation ledge. AsAo = ascending aorta; Innom A = innominate artery; LCA = left carotid artery; MPA = main pulmonary artery; LPA = left pulmonary artery; DsAo = descending aorta. (Specimen courtesy of Debra Kearney, M.D.)

is almost always located just beyond the origin of the left subclavian artery, although involvement of the origin of the left subclavian artery is not unusual. A longer segment narrowing, described as tubular hypoplasia of the aorta, is a combination of small diameter and abnormal length; it can involve the transverse aorta and isthmus and does not invariably produce obstruction. Most commonly, however, true tubular hypoplasia of the transverse aorta occurs with additional isthmic narrowing and stenosis (true coarctation).[8] In this context, definition of the normal aortic arch and its segments should be reviewed to avoid confusion with terminology (Fig. 80–4). Criteria for length of the segments of the aorta and diameter of the segments compared to the ascending aorta is useful in describing departures from normal.[9] The normal aorta begins at the aortic valve and changes in its direction as it ascends from a posterior inferior location to an anterior superior location, where it gives rise to its first branch, the right innominate artery. The transverse arch is that segment giving rise to the right innominate, left carotid, and left subclavian arteries. The transverse arch is usually subdivided into its distal segment between the left carotid and the left subclavian artery and the proximal segment between the innominate vessel and the left carotid artery. The isthmus of the aorta is the term reserved for the portion of the aorta between the origin of the left subclavian artery and insertion of the ductus arteriosus or ligamentum, with the descending aorta beginning just beyond the isthmic segment. Using this terminology, then, the discrete curtain lesion of coarctation is found in the isthmus of the aorta (Fig. 80–5).

Applying normal standards to infants, no defined segment of the aortic arch (proximal segment, distal segment, or isthmus) exceeds 5 mm in length. Compared with the ascending aortic diameter the relative segment diameters should be as follows: proximal aortic arch, 60%; distal aortic arch, 50%; and isthmus, 40%. It is when these conditions are not fulfilled that true segmental hypoplasia of the infant aorta is present.

ASSOCIATED MALFORMATIONS

A congenitally bicuspid aortic valve is the most frequent additional malformation occurring in patients with coarctation of the aorta. Estimates of frequency of this association have varied widely, from 13% to 85%.[10,11] In a review by Roberts[12] of 85 cases of bicuspid aortic valve, only five patients had additional coarc-

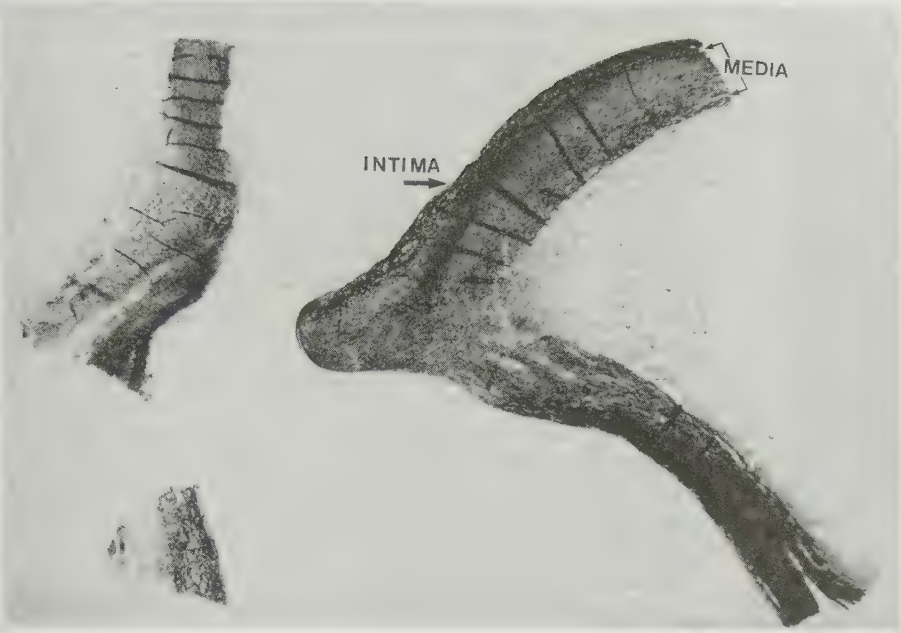

Fig. 80–2. Microscopy specimen of coarctation ledge composed primarily of media. Thin intimal covering can be seen in this section.

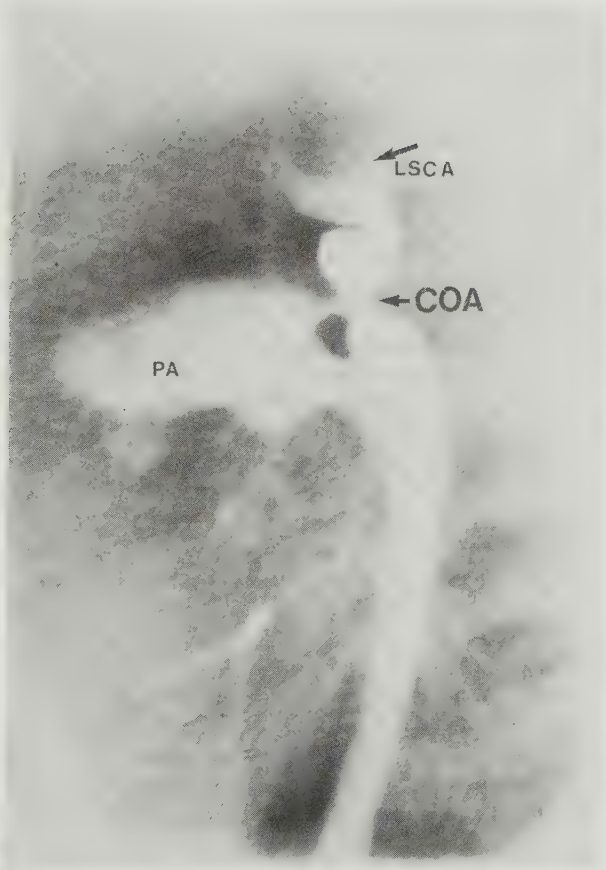

Fig. 80–3. Lateral angiogram of a 1-year-old patient with coarctation. The injection was made into the aorta above the coarctation ledge. Juxtaductal coarctation (COA) is outlined. Left-to-right ductal shunting occurs with opacification of pulmonary artery (PA). LSCA = left subclavian artery.

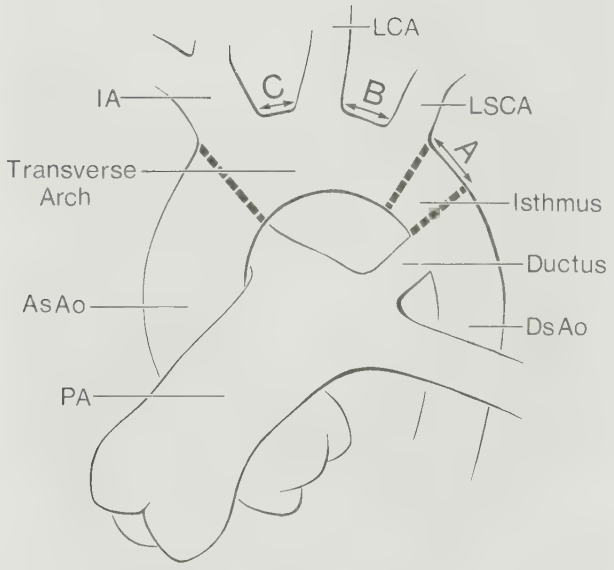

Fig. 80–4. Nomenclature for segments of the aorta (see text). PA = pulmonary artery; AsAo = ascending aorta; IA = innominate artery; LCA = left carotid artery; LSCA = left subclavian artery; DsAo = descending aorta. Portions labeled A, B, and C are measured segment lengths referred to by Moulaert which in infant aorta do not exceed 5 mm in length; these also correspond to the most common sites of arch interruption and locations for diameter measurements to interpret arch "hypoplasia." (Redrawn from Moulaert, A.J., Bruins, C.C., and Oppenheimer-Dekker, A.: Anomalies of the aortic arch and ventricular septal defects. Circulation, *53*:1011, 1976.)

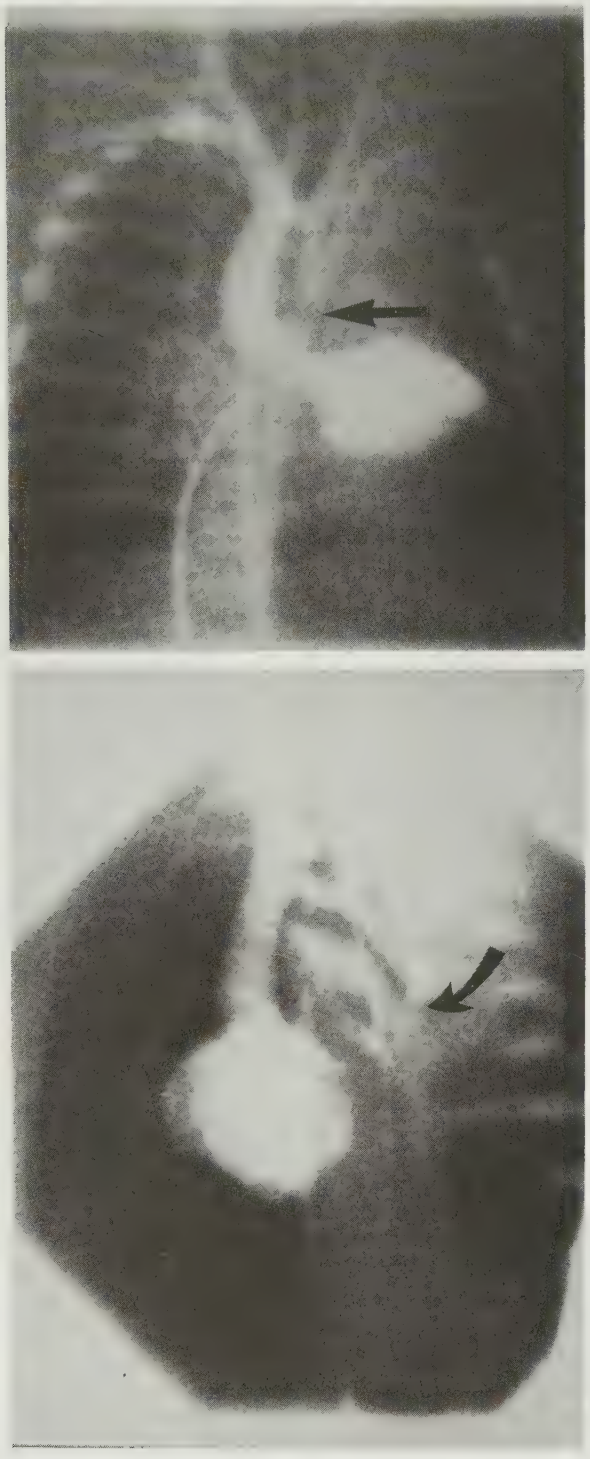

Fig. 80–5. Unusual isolated coarctation in a newborn with Ellis-van Creveld syndrome. There is hypoplasia of the transverse arch and elongation of arch segments. The isthmus is short, and a tight isthmic coarctation is identified (arrows).

tation of the aorta, attesting to the common occurrence in the adult population of isolated bicuspid aortic valve.

The exact anatomy of the bicuspid aortic valve seen in association with coarctation is a subject for continued discussion. Based on early autopsy descriptions, two types of bicuspid valves were most commonly identified[13]; 28 of 46 bicuspid valves had two cusps, often of large size with no identifiable raphe; 18 of 46 bicuspid valves were distinct in having a raphe almost invariably marking a line of fusion between the right and left coronary cusps. The relative size of the two leaflets was not emphasized. More recently, evidence has been offered that the bicuspid valve seen in association with coarctation is unique in that it is "equally bicuspid"—that is, it is more likely to have two cusps closely similar in size.[14]

Inclusion of bicuspid aortic valve makes left-sided cardiac malformations relatively common in their association with coarctation of the aorta. The additional spectrum of mitral valve anomalies found in patients whose primary diagnosis in life was coarctation is chronicled by Rosenquist.[15] A mitral valve of normal size and anatomy was found in only nine of 53 specimens examined, with an unexpected high frequency of variation in mitral valve size, restriction to the free margins of the anterior leaflet, abnormal apposition of papillary muscles, or true parachute mitral valve found in the remainder. Coexistence of multiple sites of left heart obstruction to include coarctation of the aorta constitute "Shone's syndrome."[16]

Associated intracardiac defects seem overrepresented among patients with true coarctation plus hypoplasia of the aortic arch and in fact are regarded by some to represent the "coarctation syndrome," with systemic right ventricular pressure and ductal right-to-left shunting. All types of ventricular septal defects occur with coarctation, with a frequency distribution similar to that of ventricular septal defect (VSD) alone.[17] Often, the orientation of great vessels arising from the heart with relation to the VSD, combined with additional left ventricular outflow obstruction, further allow augmentation of pulmonary flow and reduction of prograde aortic flow. In addition to the defects already mentioned, atrioventricular canal has a higher than expected incidence of associated aortic coarctation.[18] Cyanotic congenital defects of the heart may also be accompanied by coarctation,[19,20] including truncus arteriosus and transposition of the great arteries, particularly when there is overriding of the pulmonary artery and a subpulmonic VSD (Taussig-Bing anomaly).

EMBRYOLOGY

According to the theory formulated by Skoda in 1841, coarctation was thought to be a malformation that became manifest postnatally after closure of the ductus arteriosus.[21] The Skodaic theory was based on the observation that smooth muscle from the ductus extended into the aorta so that postnatal ductal constriction would place traction on the aorta and narrow the site of insertion of the ductus. This theory does not explain the location of a shelf-like protrusion of the media rising on the wall opposite from ductal insertion. In spite of agreement that ductal closure can "unmask" a coarctation lesion,[22] it is necessary to propose pathophysiology that during intrauterine development would result in the formation of a coarctation shelf lesion.

Morphologically, the ductus, like other arteries, has a wall com-

posed of intima, media, and adventitia. Essentially, the ductus is a muscular artery, as the media is recognized to consist of smooth muscle cells, and when contrasted with the aorta is deficient in elastic lamellae. Histologic study allows recognition of "ductal tissue" and an atypical extension of ductal tissue "like a sling" into the aorta is not only characteristic of coarctation but thought to be contributory to narrowing of the aorta with normal ductal closure.[8]

The occurrence of discrete coarctation in the embryologically complex area near the junction of the third, fourth, and sixth arches has led to theories that depend on blood flow in utero and the timing of insult so that a wide spectrum of conditions, from mild coarctation through interruption of the aortic arch, could result. In utero, the majority of the volume of left-sided cardiac output is distributed to the upper body, leaving only a small amount to traverse the isthmus to join the large volume of flow crossing right to left through the ductus and subsequently to the placenta. The narrow caliber of the isthmus of the aorta in the fetus and newborn infant reflects the low volume of flow through this segment prenatally.[23] The discrepancy in size between the isthmus and other portions of the aorta is not usually apparent after two months of postnatal life. Any alteration in intrauterine flow patterns that would further divert flow from the ascending aorta and its branches into the right ventricle and by way of the ductus to the descending aorta could further exaggerate the normally small caliber of the isthmus and result in true underdevelopment of this segment, which would be apparent after birth.[24] The attraction of this theory is that vessel size is proportional to blood flow and that measured dimensions of the great vessels reflect the pathophysiology.

Imprecise terminology has allowed confusion in distinguishing between underdevelopment of an aortic segment and true coarctation. The term *tubular hypoplasia* should be used to describe a long, uniformly narrow segment of the aorta variably found in the proximal or distal aortic arch or isthmus, which is not necessarily, and usually is not, obstructive; the media of the aorta in these regions is normal. In contrast, true *coarctation* results from an abnormality of the media, most commonly in the isthmic region, which produces stenosis. These abnormalities frequently coexist. It is important to recognize coarctation as a separate entity because of its obstructive nature; true tubular hypoplasia is important to recognize because of its high association with other severe congenital heart defects.

It is not easy to explain in all instances an embryologic event that would result in the usual discrete juxtaductal coarctation of the aorta without additional arch hypoplasia; however, the high incidence of associated bicuspid valve has led some authors to propose that this may be sufficient to alter left ventricular output in utero to a mild degree and allow development of the shelf lesion of coarctation in the aortic isthmus without attendant severe underdevelopment of any other segment of the aorta.

The pathogenesis of coarctation is still debated, although the many causative factors suggested could be reconciled. Altered intrauterine flow pattern, differing in degree, would contribute to prenatal arch hypoplasia and molding of the coarctation shelf. Progression in the degree of severity of coarctation may be the result of progressive intimal thickening added to the coarctation ledge. The protuberance of media into the lumen (coarctation shelf) is pulled toward the contralateral wall with ductal closure much like a cork fits into the mouth of a bottle (Fig. 80–6).

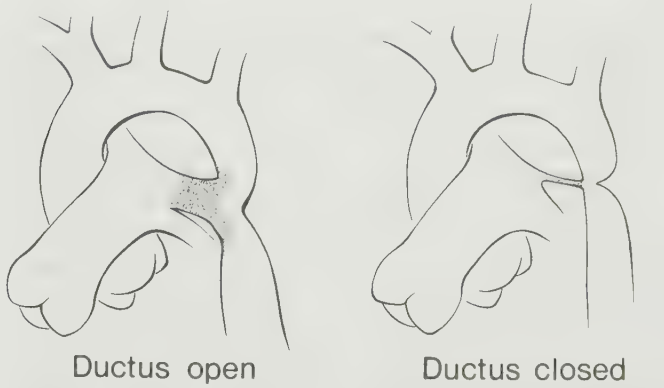

Fig. 80–6. Influence of ductal closure on coarctation shelf. The coarctation ledge becomes obstructive with ductal constriction. Stippled area represents concept of extension of ductal tissue into aortic wall (see text).

EPIDEMIOLOGY AND GENETICS

Coarctation of the aorta is not a rare defect in the spectrum of congenital heart disease. In surveys of patients recognized to have congenital heart disease (independent of cases of related bicuspid aortic valve and mitral valve prolapse), this abnormality accounts for 5 to 8% of patients. There is a striking male-to-female ratio for discrete coarctation of the aorta, with males representing over two thirds of patients in most series. The exception is that of abdominal coarctation, in which case a female preponderance is usual. In addition, the male-to-female ratio is less evident in infants with coarctation syndrome. Although it is rare to observe a true racial difference in most forms of congenital heart disease, there is some suggestion that coarctation is less common in children of Asiatic countries, who share a similar ancestral origin with North American Indian children. It is not clear if this is a matter of detection. An increase in seasonal occurrence of coarctation of the aorta with a peak incidence in September and November births has been proposed and possibly is indicative of some environmental influence.

Turner's syndrome is discussed fully in Chapter 144. Patients with the full XO Turner's syndrome with ovarian agenesis and short stature are said to have a high incidence of coarctation in 15 to 20% of cases. This is seldom true with mosaic forms of Turner's or Turner's phenotype. A rare familial pattern to coarctation has also been reported.[25]

PHYSIOLOGY

The major physiologic effect of coarctation of the aorta is to increase the afterload of the left ventricle. During ejection, the left ventricle must empty against the resistance mechanically imposed by the obstruction as well as against the increase in arterial pressure that has developed proximal to the coarctation. Consequently, systolic wall tension in the left ventricle is increased, with development of left ventricular hypertrophy. Blood pressure in the aorta and the branches of the aorta that arise above the coarctation is increased and although variable in degree, systolic hypertension above with systolic hypotension below the constricted area are present in all cases of aortic coarctation. The alterations in the arterial waveforms above and below the coarctation can be explained on the basis of differing degrees of narrowing of the aortic lumen (see Fig. 80–19). In the experimental

coarctation model well examined by Gupta and Wiggers,[26] an understanding of these changes is systematically presented. The arterial pressures are not significantly affected until the aortic lumen has been reduced by 45 to 55%. The first change seen is an increase in systolic pressure above the obstruction with a later increase in diastolic pressures above the obstruction but to a lesser degree than that of the systolic increase, allowing for progressive widening of the pulse pressure above the coarctation. Below the coarctation there is a gradual decrease in systolic pressure as well as diastolic pressure.

The greater decrease in systolic compared with diastolic pressure results in a narrow pulse pressure below the coarctation. Comparison of waveforms reveals that the pulse contour measured below the obstruction rises and falls more slowly than the pulse contour in the proximal aorta, resulting in a delayed slow upstroke, rounded broad peak, and a smooth declining slope during diastole.[27] The clinical recognition of a "delay" between radial and femoral pulses is not attributed to a delay in transmission from the aorta to the femoral artery. Rather, the tactile sensation of diminished delayed femoral pulses is explained on the basis of the slower rate of rise of the pulse wave, the difference in the timing of the peaks of these curves, and the narrow pulse pressure.

By the time the aortic lumen is moderately constricted, the femoral arterial systolic pressure no longer exceeds the aortic pressure. The constricted area serves to dampen the pulse wave as it passes through this area and the less forceful impact of the pulse waves is used to explain that the standing wave is not created downstream; the summation of pressures on the anacrotic limb of the pulse contour is prevented, resulting in the lack of systolic overshoot, which is normally recognized in a femoral waveform recording.

It is known that equivalent degrees of constriction may not be reflected by the same measurement of blood pressure elevation nor be accompanied by the same alteration in femoral pressures, owing to the development of collateral vessels. More severe hypertension and pulse discrepancy may be seen in a young child compared with that same patient who, when collateral vessels develop in later childhood, may have less hypertension and the re-appearance of palpable but diminished femoral pulses. Collateral vessels bypass the coarctation and channel flow to the lower body. The collaterals primarily arise from branches of the subclavian vessels and involve internal mammary arteries, intercostal arteries, and spinal arteries (Fig. 80–7).[28]

It is an oversimplification to attribute the hypertension that is seen with coarctation of the aorta solely to mechanical obstruction. Equally important to the degree of hypertension is the reduced distensibility of the aorta and the capacity of the vascular bed proximal to the coarctation. Additional theories implicating a resetting of baroreceptors in the aortic arch[29] and the possible contribution of a renal factor stimulated by decreased renal blood flow[30] are offered. There is no consistent evidence of a functional abnormality of the kidneys in coarctation, and determinations of peripheral plasma renin activity give conflicting results about whether an additional mechanism for production of hypertension involves the renin-angiotensin system.[31] It can be safely stated that renal factors are less important in the young patient with coarctation.

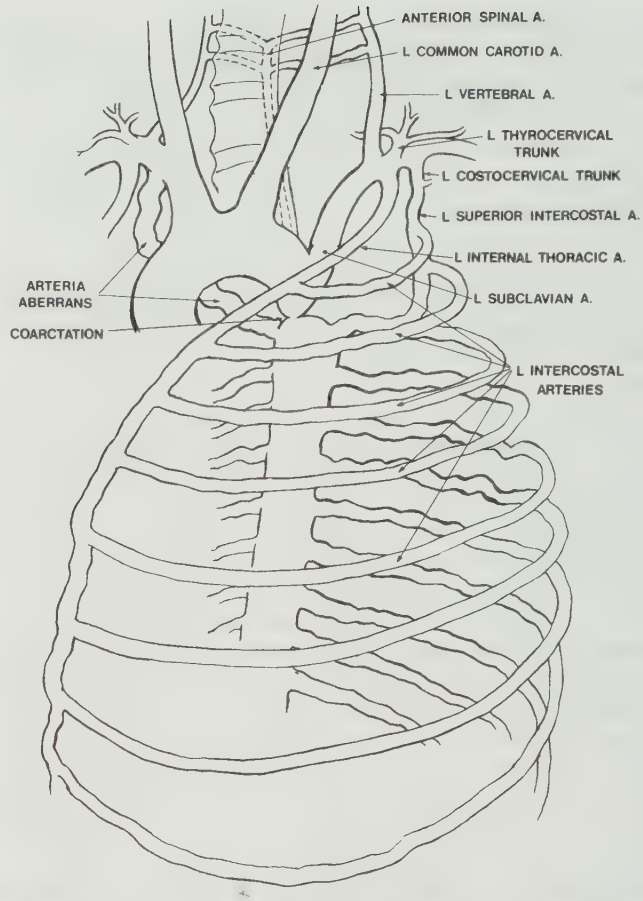

Fig. 80–7. Collateral circulation in aortic coarctation. The primary source of collaterals is from the subclavian artery via three branches: thyrocervical trunk, costocervical trunk, and internal thoracic arteries. Intercostal arteries (fourth and below) communicate directly with the aorta beyond the coarctation as well as with the internal thoracic artery and are responsible for rib-notching. (Intercostals 1 to 3 join superior intercostal artery, which in turn connects with aorta.) The anterior spinal artery receives vertebral artery communications and is involved in collateral flow to bypass the coarctation. The most constant collateral seems to be the large arteria aberrans.

CLINICAL FEATURES

The discussion of clinical features will be divided into two parts: patients who present past infancy (the more common occurrence), followed by coarctation syndrome in infancy. Clinical manifestations in both groups depend on the association of coarctation with other defects but the unique effects of coarctation of the aorta on the circulation will be emphasized.

Coarctation Past Infancy

Clinical recognition of coarctation should be obvious when blood pressure readings are obtained from all four extremities; hypertension above the obstruction and decreased blood pressure below the obstruction are the hallmarks of diagnosis. Most individuals with isolated coarctation of the aorta have no cardiac symptoms. Minor complaints of cold feet and leg cramps are seemingly volunteered more often from observant parents; however, the frequency with which these complaints may be elicited by direct inquiry even from patients without coarctation make their rele-

vance uncertain. An actual history of claudication is rare, but when it is present and a complaint of sharp pain in the lower extremities is said to limit exercise, the diagnosis of abdominal coarctation should be considered with knowledge that collateral circulation is not as easily established in the abdomen. Paresthesia, pain, and muscle weakness may occur in the lower extremities, but rather than being reflective of poor blood flow, may actually result from a dilated and tortuous anterior spinal artery compressing the spinal cord directly or one of its branches impinging upon a nerve root exiting the vertebral canal. Nose bleeds and headaches are additional nonspecific symptoms accompanying coarctation of the aorta. Unilateral headaches, particularly of unusual severity, are rarely indicative of cerebral aneurysm in association with coarctation but should prompt a full neurologic evaluation. Older clinical reports mentioned plethora and flushing of the face as well as delayed healing of lower extremity wounds as accompaniments of aortic coarctation.

Physical Examination

The outstanding physical finding is that of striking inequality in the strength of upper extremity pulses compared with the small volume or absent lower extremity pulses. This is further substantiated by blood pressure measurements indicating hypertension in the upper extremities while lower extremity pressures are difficult or impossible to record. Hypertension, though invariably present, may not directly reflect the severity of obstruction and may not be extreme. A body build commonly seen in adolescence features a sturdy, well-developed upper torso in contrast to a thinner lower body with trim hips and legs. The characteristic appearance of patients with Turner's syndrome—short stature, webbed neck, and shield chest—presents another clinical profile that should raise the question of co-existence of coarctation of the aorta. Funduscopic examination has revealed a peculiar "corkscrew" appearance to retinal arteries in a pattern unlike hypertensive retinopathy (Fig. 80–8).

Unequal blood pressures between the two arms may be the result of the peculiar position of one or both subclavian arteries in relation to the coarctation. A right arm pressure higher than the left arm pressure suggests that the coarctation is proximal to the left subclavian artery or involves the origin of the left subclavian artery. When left arm pressures are higher than right in the presence of coarctation, an anomalous origin of the right subclavian artery arising beyond the coarctation may be the explanation. The rare occurrence of origin of both subclavian arteries in the low-pressure zone beyond the coarctation makes clinical recognition of coarctation from blood pressure measurements difficult, although palpation of bounding carotid pulses contrasting with weak femoral pulses could suggest the diagnosis of coarctation to the astute clinician.

Examination of the patient with coarctation of the aorta should be systematically performed with an attempt to explain the auscultatory findings rather than with the prejudice that a particular murmur is characteristic of coarctation. A murmur may be generated from the coarctation itself and would serve as evidence that atresia of the lumen of the aorta is not present. This murmur is best heard in the auscultatory areas corresponding to the thoracic location of the coarctation (the left infraclavicular area, axilla, and posteriorly over the left chest medial to the scapula). The murmur sometimes peaks late in systole and extends into diastole when a persistent coarctation gradient is present. Continuous murmurs generated at the site of distal connection of collateral vessels may also be present throughout the anterior and posterior chest. Particularly when detected in the left chest, these murmurs could be confused with a murmur originating from the area of coarctation. Occasionally, with severe coarctation and low cardiac output state or with complete atresia of the lumen, a murmur is absent. Presence of an aortic ejection click and an ejection murmur in the aortic area should make the clinician suspicious of an additional bicuspid aortic valve with aortic stenosis. The murmur of aortic insufficiency may be present as well and lead to additional concern about an abnormal aortic valve. A thrill at the right upper sternal border may be further evidence of aortic valve stenosis. However,

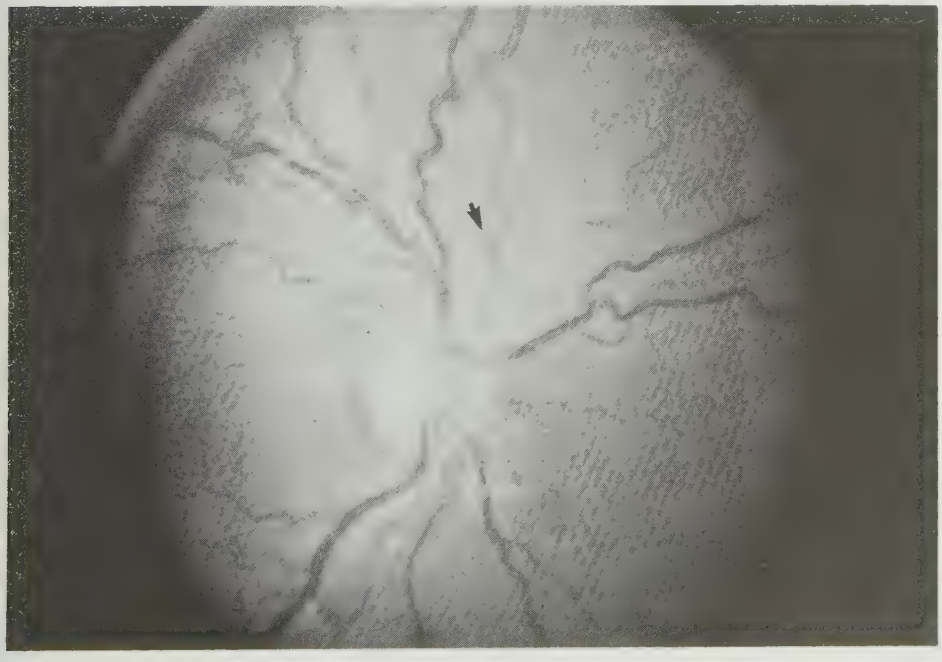

Fig. 80–8. Eyeground in a 12-year-old boy with coarctation. True arteries emerging from optic disk are more tortuous with "corkscrew" vessel shown (arrow). Pattern is different from hypertensive retinopathy at older age. Larger, darker vessels are veins.

a thrill with prominent pulsations in the supersternal notch and carotids can be present with coarctation of the aorta alone. Additional diastolic murmurs over the left axilla and at the apex of the heart could be evidence of diastolic flow across the coarctation but additionally would raise the suspicion of turbulent diastolic mitral flow associated with mitral valve abnormalities.

The presence of pulsating intercostal arteries as a clinical finding is a function of age. Palpable or visible collaterals in the interscapular region are rare in childhood and often, because of early elective surgery, do not develop. Forceful arterial pulsations visible in the neck can be present at a young age.

Simultaneous palpation of brachial and femoral vessels is helpful. In the presence of mild coarctation or with well-developed collaterals, femoral pulses can be felt. If simultaneous palpation of upper and lower extremity pulses is not conducted with recognition of the apparent delay in femoral pulses, mild coarctation may be missed. This sign can be subtle, however, and the inexperienced examiner who fails to measure pressures is likely to miss cases of mild coarctation. The first heart sound is generally normal. It can be followed by a high-frequency systolic ejection click when bicuspid aortic valve is present or if there is significant dilation of the aortic root in the presence of a normal tricuspid aortic valve. The second heart sound with isolated coarctation is usually characterized by normal respiratory variation, but the aortic component may be increased in intensity with a "ringing" quality due to the systemic hypertension.

Fig. 80–9. AP chest film from a 12-year-old boy. Rib-notching is seen best on the undersurface of right sixth and eighth posterior ribs and left fourth and eighth posterior ribs (arrows). "3 sign" (see text) is also apparent.

Electrocardiogram

Even in the presence of significant aortic coarctation, the electrocardiogram (ECG) is often normal in children. One expected change is increased voltage in the left precordial leads. True left ventricular hypertrophy is apparent with more severe or longer standing coarctation. Electrocardiographic evidence of right bundle branch block is found in approximately 50% of adults and older children and is said to reflect a stage in progression from neonatal right ventricular hypertrophy.[32]

Exercise electrocardiography may unmask ST segment and T wave changes reflective of ischemia; however, a normal exercise effort and electrocardiographic recording during exercise are not unusual.

Chest Roentgenography

Typically, the radiologic examination of an older child with coarctation shows normal heart size; less frequently the heart is mildly enlarged with a left ventricular contour (Fig. 80–9). Pulmonary vascular markings are normal unless there is an associated intracardiac shunt or manifest left ventricular failure. A dilated ascending aorta visible to the right of the sternum may accompany coarctation of the aorta even in an absence of additional aortic valve disease. The aortic knob may be inconspicuous or prominent. In some patients there is radiographic evidence of pre- and post-stenotic dilation seen as a double aortic curve, referred to as the "3 sign," along the left paramediastinal shadow in the AP view. The pre- and post-stenotic dilation is exhibited as a mirror image to that described when barium in the esophagus outlines the dilation above and below the coarcted area referred as the "E-sign" (or "reversed 3 sign"). The left anterior oblique projection may be used to enhance recognition of the post-stenotic dilation just below the level of coarctation as it produces anterior displacement of the barium-filled esophagus.

Rib-notching is practically pathognomonic of thoracic coarctation of the aorta (see Chapter 44, Fig. 44–26).[33] The incidence of rib notching increases with age because erosion of the ribs by the dilated intercostal collateral vessels progresses slowly. The erosion, or scalloping, of the undersurface of the ribs (technically in the costal grooves) is most commonly seen bilaterally in the fourth to ninth posterior ribs.[28] Unilateral rib-notching is found when one subclavian artery arises below the coarctation in the low-pressure zone with sparse development of collaterals on that side. Retrosternal scalloping by displaced and enlarged collaterals is an analogous process seen on the lateral chest film. Rib-notching occurs in 70% of patients aged 6 to 41 years and in the majority of patients over age 20 years. It is extremely rare to detect rib-notching in infancy. Rib-notching below age 5 is uncommon, although in one study it was visible in 14% of patients between 1 and 4 years of age.[34]

Echocardiogram

The clinical diagnosis of coarctation of the aorta is easier to make than the echocardiographic diagnosis. The role of M-mode echocardiography in this condition is limited to possible recognition of bicuspid aortic valve as well as estimations of left ventricular wall thickness and shortening fraction. Recognition of bicuspid aortic valve accompanying coarctation is not available with 100% accuracy even when a technically satisfactory view of the aortic root and aortic valve motion is available.[35] M-mode computation of an abnormal "eccentricity index" was used to describe the eccentric location of the point of diastolic coaptation that often accompanies bicuspid aortic valve closure, although

"equally bicuspid" valves may be difficult to identify by this method. Left ventricular wall thickness can be measured and is reflective of increased afterload. A formula used to estimate left ventricular pressure is useful in this lesion, analogous to its use in estimating left ventricular pressure with aortic stenosis.[36] This formula is expressed as:

$$\text{LV systolic pressure (mm Hg)} = \frac{225 \text{ mm Hg} \times \text{LV end systolic wall thickness (mm)}}{\text{LV end systolic dimension (mm)}}$$

Two-dimensional echocardiography from the usual echocardiographic windows on the thorax again gives evidence of left ventricular measurements reflecting increased afterload. Imaging of the region of the coarctation, however, is more difficult and best sought from the suprasternal and high left parasternal approaches (Fig. 80–10).[37] The difficulties in examining the aorta throughout its course have been described by knowledgeable echocardiographers. A particularly high level of skill is necessary to view the area of origin of the left subclavian artery and descending aorta to look for the usual location of coarctation. The suprasternal notch imaging requires support of the shoulders and hyperextension of the neck with attendant discomfort to the patient, rendering these studies difficult in an unsedated frightened child. It is frequently necessary to sedate young infants for this procedure. The particular utility of these views is increased when imaging can be coupled with Doppler echocardiography. The major justification of the effort and time required to obtain echocardiographic studies is to have additional confirmation that the coarctation is indeed in the usual location, which can eliminate the need for catheterization and permit confident recommendation to the surgeon planning a traditional incision for coarctation repair. Using the segmental approach to echocardiography, it is important to look at mitral valve anatomy, as well as to measure left ventricular wall thickness and shortening fraction and to view the left ventricular outflow tract looking for additional sites of obstruction. The descending aorta can be imaged in the long axis view in the abdomen with reduced pulsations generally observed in cases of coarctation of the aorta.

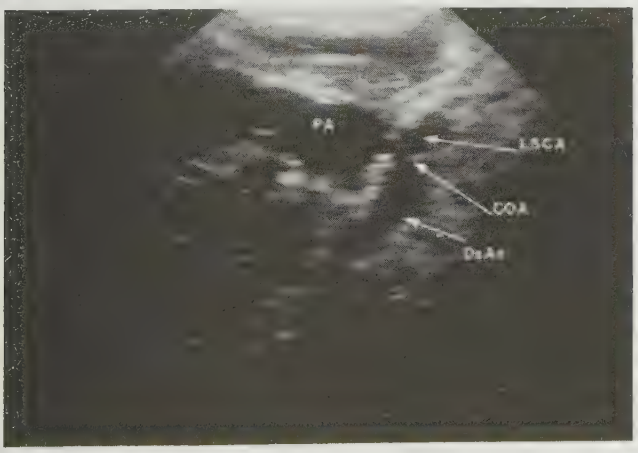

Fig. 80–10. 2-Dimensional echocardiography of a typical coarctation viewed from the high left sagittal plane. The posterior coarctation ledge (COA) is visualized beyond the origin of the left subclavian artery (LSCA) and oriented toward the ductus arteriosus, which remains patent. DsAo = descending aorta; PA = pulmonary artery.

With pulsed Doppler echocardiography, the sample volume can be placed under image direction in the area just above the coarctation site. One will find a typical pattern of diastolic runoff proximal to the coarctation caused by the persistent gradient across the coarctation in diastole. As the sample volume is moved across the area of coarctation into the descending aorta, there is a rapid increase in systolic flow velocity, which usually exceeds the Nyquist level for pulsed Doppler. A continuous-wave Doppler study can then be performed with a probe directed in the same manner across the coarctation. The continuous-wave Doppler signal (Fig. 80–11) across the area of coarctation is unique in revealing two types of flow: one with a low velocity reflecting flow through the area above the coarctation and the other a high velocity outer envelope generated by rapid velocity flow through the narrow area.

Two-dimensional echocardiography has also improved the recognition of bicuspid aortic valve, though a confident diagnosis may not always be made.[38] Since coarctation necessitates endocarditis prophylaxis indefinitely, the recognition of a bicuspid valve that functions well may not be of considerable importance. The necessity of inspecting the aortic valve in systole as well as in diastole is emphasized with the inability of the leaflets of the bicuspid valve to open completely in systole, giving a fish-mouth appearance to the opened aortic valve. The coapted leaflets in diastole may transcribe a single line of closure across the aortic root and occasionally, the position of the raphe can also be seen. The certainty with which this diagnosis can be made by echocardiography depends on the quality of image obtained as well as the experience of the echocardiographer. The high success of detection reported in the literature may not be easy for every center to reproduce.[39]

Magnetic Resonance Imaging

The role of magnetic resonance imaging (MRI) in prospective identification and followup of patients with coarctation of the aorta is not yet defined, but new reports attest that this technique allows satisfactory visualization of the coarctation area (Fig. 80–12).[40] In young children, sedation must be used for MRI. Comparing MRI and other techniques with respect to the cost, patient risk, and operator time, it would seem that echocardiography is still superior[41]; however, the confidence of diagnosis may be greater with the actual imaging available for inspection after MRI. If it has been decided during the management of the patient that catheterization is indicated, MRI evaluation would not be necessary. Clinical applications of MRI are discussed in Chapter 51. The utility of MRI may be its use in the followup of patients with coarctation to screen for distortion of the aorta after balloon dilatation, to identify aneurysm formation at an early stage, and to allow serial measurements of aneurysms that are recognized after surgical repair.[42] As usual, patients are disqualified from having an MRI study safely performed if they have a pacemaker and wires in place or if metallic clips have been previously placed in the thorax. The usual stainless steel sternotomy wires present in patients with coarctation who have had additional lesions approached by way of an anterior thoracotomy do not disqualify a patient from having an MRI study.

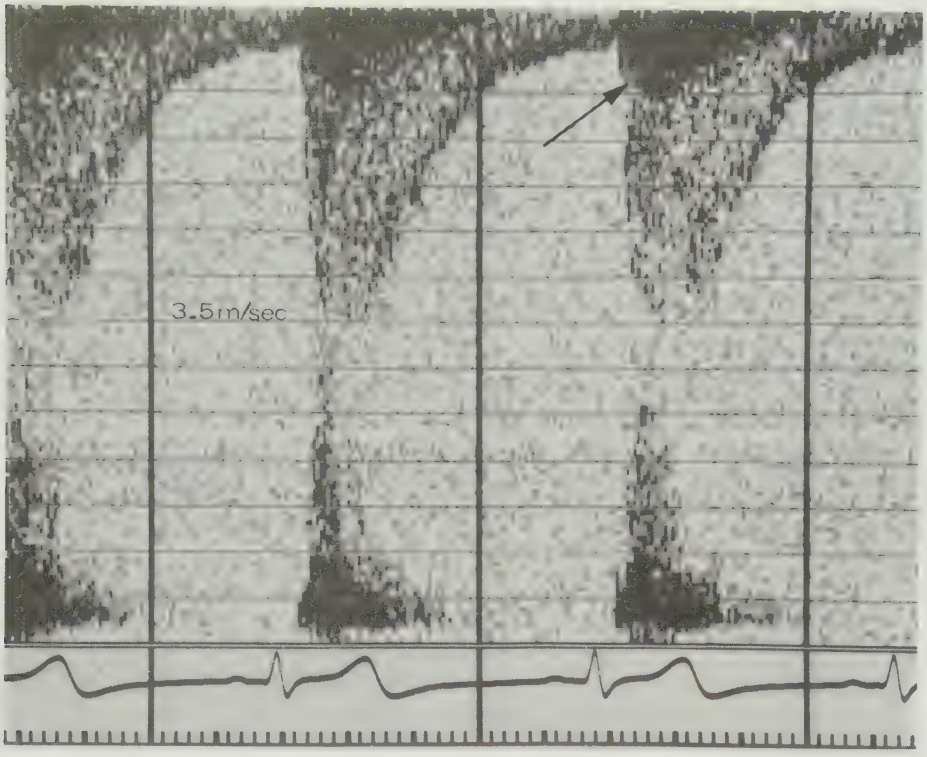

Fig. 80–11. Continuous-wave Doppler flow pattern obtained from a patient with aortic coarctation. High-velocity (3.5 m/sec) outer envelope represents flow moving through coarcted segment. Lower velocity, dense inner envelope (arrow) represents flow traveling at a lower velocity in the aorta, above the obstruction.

Fig. 80–12. Magnetic resonance imaging (MRI), parasagittal T_1, weighted image through thoracic aorta (similar to lateral view angiogram) in a 4-year-old boy. Findings were interpreted as dilation of the ascending aorta, narrowing of the transverse arch, and a "web coarctation" represented by increased signal intensity across the lumen of the aorta immediately beyond the origin of the left subclavian artery. Complete atresia of the lumen is suspected based on additional Doppler studies.

Cardiac Catheterization and Angiography

The role of catheterization in evaluating patients with isolated coarctation has been variously described as either "nonessential," "required for definition of anatomy," or more recently, "therapeutic." When the precise diagnosis of coarctation and associated lesions can be accurately and confidently made, surgery can be scheduled without catheterization. It is possible that preoperative recognition of severe hypoplasia of the aorta in addition to coarctation might influence postponement of operation although most variations in coarctation anatomy can be successfully managed by the surgeon at the time of inspection. Concern that the coarctation might be in an atypical location or that coarctation sites may be multiple may impose enough doubt on the cardiologist that catheterization is performed. In particular, catheterization is useful in cases where there is absence of rib-notching, there is an inability to confidently image the coarctation on echocardiography, and when important associated defects cannot be definitely excluded or evaluated by noninvasive techniques. Catheterization is sometimes justified by the need to determine if there are "adequate collaterals" for surgery. This position might be tenable if rib-notching is unexpectedly absent in the older patient, or if reoperation for coarctation is projected and knowledge of collateralization will influence surgical perfusion techniques.

When catheterization is performed, it should consist of complete right and left heart catheterization. The feasibility of a prograde approach to the left heart has been improved with wider application of the transseptal method for entering the left heart in cases without a patent foramen ovale (Fig. 80–13). With a prograde left heart study, the aortic valve can and should be crossed from the left ventricle with a balloon catheter to allow angiography of the aorta and a withdrawal record from the aorta to the left ventricle to search for coexistent aortic valve stenosis. The retrograde arterial

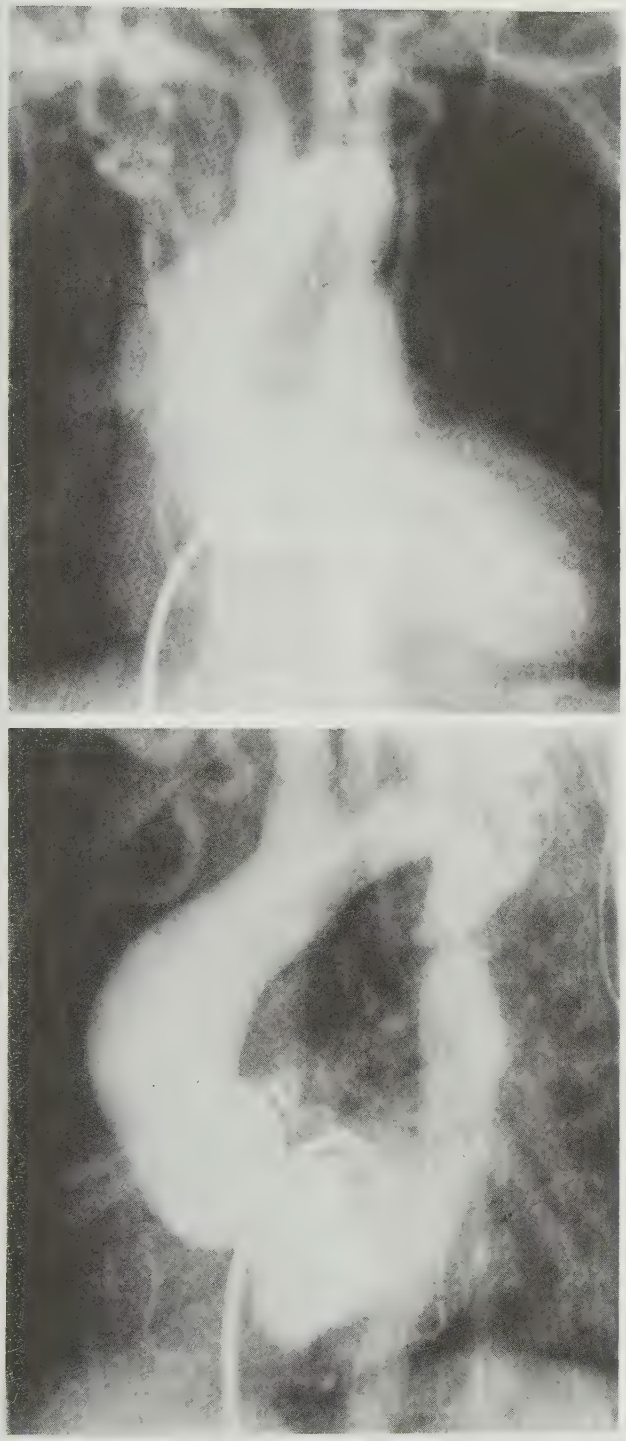

Fig. 80–13. Coarctation of aorta-LV angiogram in an 8-year-old boy. Dilation of the ascending aorta and well-developed collateral circulation are apparent in AP (top) and LAT (bottom) cine frames. The tortuosity of the aorta and its course make echocardiographic imaging difficult. The left ventricle was entered using a transseptal method.

approach from the femoral artery can be carefully done and is not considered to be inadvisable because of risk. However, it is difficult to enter the femoral artery in some cases because of the decreased femoral pulses. Techniques of balloon dilatation have demonstrated not only the ability to pass a catheter past the stenosis but also the safety of temporary occlusion of the coarctation lumen. The catheterization should be complete in the exclusion of other defects. Pressure tracings obtained from above the coarctation typically show elevated systolic, diastolic, and mean pressures with a widened pulse pressure (see Fig. 80–19B). Tracings from below the coarctation area appear damped, with low systolic pressures and narrow pulse pressure. Severe proximal obstruction at the aortic valve may mask the pressure gradient at the coarctation site.

Angiography with injections into the left ventricle and the aorta proximal to the coarctation are useful in recognizing associated defects demonstrating origin of arch vessels, viewing development of collateral vessels, and outlining the definitive anatomy of the coarctation segment.

Coarctation Syndrome In Infancy

Isolated discrete coarctation of the aorta is uncommonly recognized in the neonatal period.[49,50] Coarctation in infancy is often part of a more complex spectrum of heart disease producing recognizable heart failure or even catastrophic illness.[51] In "coarctation syndrome," a diffuse hypoplasia of the aorta is found in addition to the actual coarctation lesion, isthmic in location, that produces obstruction. Usually, other defects are present, commonly ventricular septal defect (VSD), resulting in systemic right ventricular pressure and flow reversal from right to left through the ductus arteriosus. Early age at presentation, difficulties in management, and a less favorable outcome further distinguish this entity from discrete coarctation in the older patient.

Additional diagnostic confusion results from the fact that some degree of narrowing of the transverse aorta and isthmus occurs in the normal infant without producing obstruction. Pulmonary hypertension occurring from any cause, particularly secondary to lung disease, allows right-to-left shunting through a persistently patent ductus arteriosus, which mimics the flow patterns seen with true infantile aortic coarctation. Several methods for measurement of the aorta have been proposed to distinguish normal tapering of the aorta from true hypoplasia (with a uniformly narrow but nonobstructive segment) from actual segmental constriction characteristic of coarctation stenosis. Taussig stated that the isthmus should not be considered to be abnormal unless it narrowed to the width of one of the carotid arteries.[6] Moulaert and colleagues concluded that the diameter at the isthmus had to fall below 40% of the diameter of the ascending aorta in order to identify important isthmic underdevelopment[9]; additional criteria for abnormal isthmic length were added. Sinha et al.[52] used autopsy and angiographic measurements to describe underdevelopment of the transverse aortic arch delineating it as a separate entity from isthmic coarctation. The findings that hypoplasia of the aorta, abnormally rapid tapering of the aortic arch, and localized coarctation are consistently present in the majority of infants ill with coarctation are supported by morphometric echocardiographic measurements.[24] The frequent association of other important intracardiac defects may further help to distinguish patients with true coarctation syndrome from ill newborns who have the normal degree

of isthmic narrowing but right-to-left ductal shunting caused by pulmonary hypertension. The rarity with which isolated coarctation, with normal aortic arch development and no additional defect, produces congestive failure in infancy has been emphasized in numerous reports.[49,51,52]

Hemodynamic disturbances in an infant with coarctation are variable but easily understood when consideration is given to the site and severity of aortic obstruction, as well as the influence of associated defects and the contribution of the patency and direction of flow in the ductus.[53]

When the coarctation ledge occurs as an isolated lesion proximal to the insertion of the ductus, the intrauterine flow patterns have not been altered to an extent that stimulus for development of collateral vessels in utero existed. A critical resistance to left ventricular emptying is imposed only after birth, when the ductus closes (see Fig. 80–6), runoff into the lower resistance pulmonary bed is abolished, and severe left-sided congestive heart failure occurs. This results in the clinical presentation of an infant in respiratory distress with severe cardiac failure. The newborn is recognized to have audible rales, gallop rhythm, hepatomegaly, peripheral edema, and a pulse discrepancy that has become apparent with ductal constriction. Because of the severe impairment of cardiac output, a murmur may not be detected until improved cardiac output has been achieved with treatment of the heart failure and reversal of shock.

If the hemodynamic pattern is altered to allow right-to-left ductal shunting there is a provision for clinical observation of differential cyanosis. The ascending aorta and its branches are supplied by fully saturated blood from the left ventricle whereas branches of the aorta below the coarctation are supplied from the pulmonary artery by way of the ductus, allowing a demarcation in color with cyanosis of the lower body compared to the upper body. This clinical impression can be substantiated by measuring a higher saturation of blood obtained from a right radial artery compared to a lower saturation obtained from the umbilical artery catheter below the coarctation. In the presence of an intracardiac left-to-right shunt, the pulmonary artery saturations may be abnormally high so that a measurable difference in saturations between upper and lower body is not as great. The reverse is also true in that with an intracardiac right-to-left shunt, upper extremity saturations may be lower and again not too dissimilar from the level of desaturation obtained from sampling below the coarctation site, although both will be decreased. Clinical recognition is further hampered by normally present acrocyanosis in response to temperature changes. Generalized cyanosis with circulatory shock in the very ill infant with coarctation of the aorta may render an evaluation of differential cyanosis more difficult. When the ductus is widely patent in an infant with coarctation, obvious clinical symptoms may not be present. However, spasmodic attacks of ashen color, fretfulness, and dyspnea may be seen with ductal closure, and may rapidly improve with ductal relaxation. These clinical presentations may be greatly altered when additional cardiac defects are present. The patient may have profound cyanosis apparent if transposition of the great vessels coexists with coarctation and ductus. In these infants, "reverse" differential cyanosis may occur, with the upper body bluer and the lower body pinker. The expected occurrence of a large ventricular septal defect in infants with coarctation syndrome may result in a presentation more typical for a large left-to-right shunt, with attendant difficulty in establishing the association of a coexistent coarctation when the ductus is widely patent.

In an infant with coarctation who has heart failure in infancy, suspicion of associated defects should be high. A less favorable response to medical therapy is recognized in this group, prompting early surgical treatment. The most important point to emphasize is the frequent anatomic and physiologic complexity of coarctation lesion in the infant age group.

The ECG of infants with coarctation of the aorta is often abnormal and usually reflects coexistent anatomic defects.[32] Isolated coarctation of the aorta in the neonate usually is accompanied by electrocardiographic evidence of right ventricular hypertrophy or right bundle branch block. Left ventricular hypertrophy and/or left ventricular strain is uncommonly seen in the neonate (Fig. 80–15), although left ventricular strain, in itself, may prompt earlier surgical management because left ventricular strain reflects the hemodynamic state of severe increase in afterload acutely imposed on the left ventricle with ductal closure. The echocardiogram in infants with congestive heart failure can show a marked increase in left ventricular wall thickness immediately after birth. Evidence of a dilated, poorly contracting left ventricle raises the question of cardiomyopathy or possible endocardial fibroelastosis; however, markedly severe left ventricular dysfunction as assessed by echocardiographic measurements may be found in the infant with coarctation of the aorta who has complete reversal of these findings after relief of the obstruction. Chest roentgenograms are altered by associated defects so that increased pulmonary vascular markings are seen with a left-to-right shunt or venous congestion may be found due to severe coarctation alone or associated left heart obstructive lesions. Rib-notching is rare in infants but has occasionally been reported when severe functional obstruction is present in utero.

Cardiac catheterization is undertaken at increased risk in the moribund infant with coarctation. When noninvasive recognition of the components of coarctation syndrome can be reliably defined with the adjunct of echocardiography, direct recommendation for surgical repair of coarctation of the aorta and either pulmonary artery banding or closure of a VSD, if necessary, can be a lifesaving approach. The success of balloon angioplasty for coarctation of the aorta in a sick infant continues to be debated and will be further discussed.[54,55]

Systemic hypertension rarely justifies surgery in infancy unless it is accompanied by severe left ventricular failure. No absolute level of hypertension has been published as being the single indication for surgery; the natural history with development of collateral vessels and a decrease in degree of hypertension supports the opinion that elective surgery for isolated coarctation in infancy is unwise if medical management is successful.

Surgical treatment of coarctation in an infant was first reported by Kirklin et al. in 1952.[56] In an infant presenting with congestive heart failure, the likelihood of associated important congenital heart disease is high; 80% have additional severe congenital heart disease. Poor response to medical management alone is the rule,[57] and in spite of the known high surgical mortality rate in infants under age 6 weeks (45%), mortality without surgery is reportedly higher (86%).[49] In our institution, infants with complex coarctation are offered immediate operation, consisting of relief of aortic obstruction, and we add pulmonary artery banding if a coexistent VSD is large, complex, or multiple.[58,59] Another approach is to

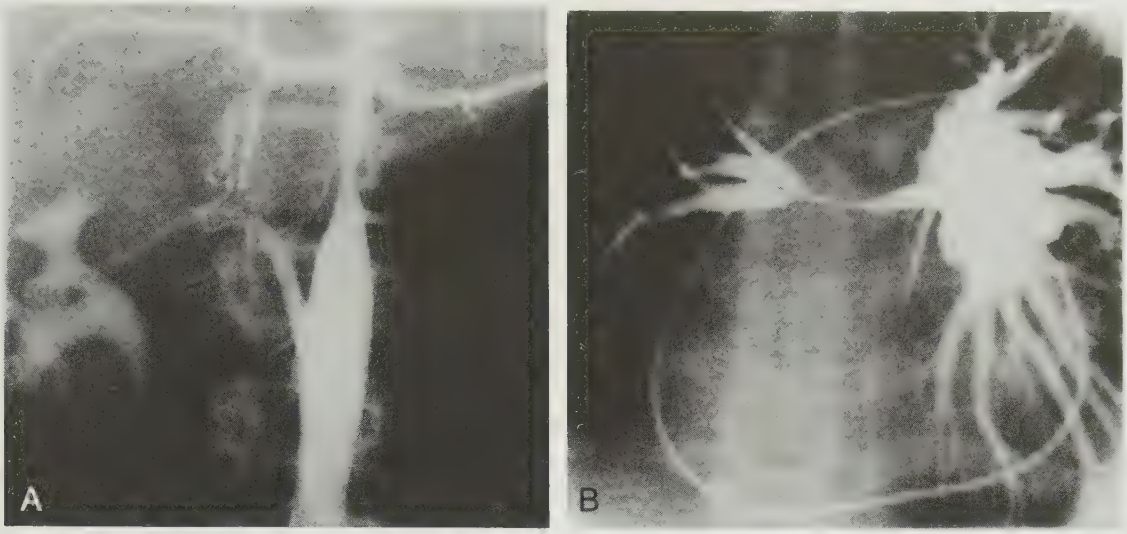

Fig. 80–14. Takayasu's arteritis in a 13-year-old girl. (A) Abdominal aortic coarctation with hourglass deformity of aorta at level of L_1. Right renal artery is stenotic. The left renal artery is not visualized owing to previous implantation of left kidney into pelvis. (B) Arteritis also affects the right pulmonary artery (RPA). Long area of severe RPA stenosis is visualized on AP angiogram with injection into main pulmonary artery.

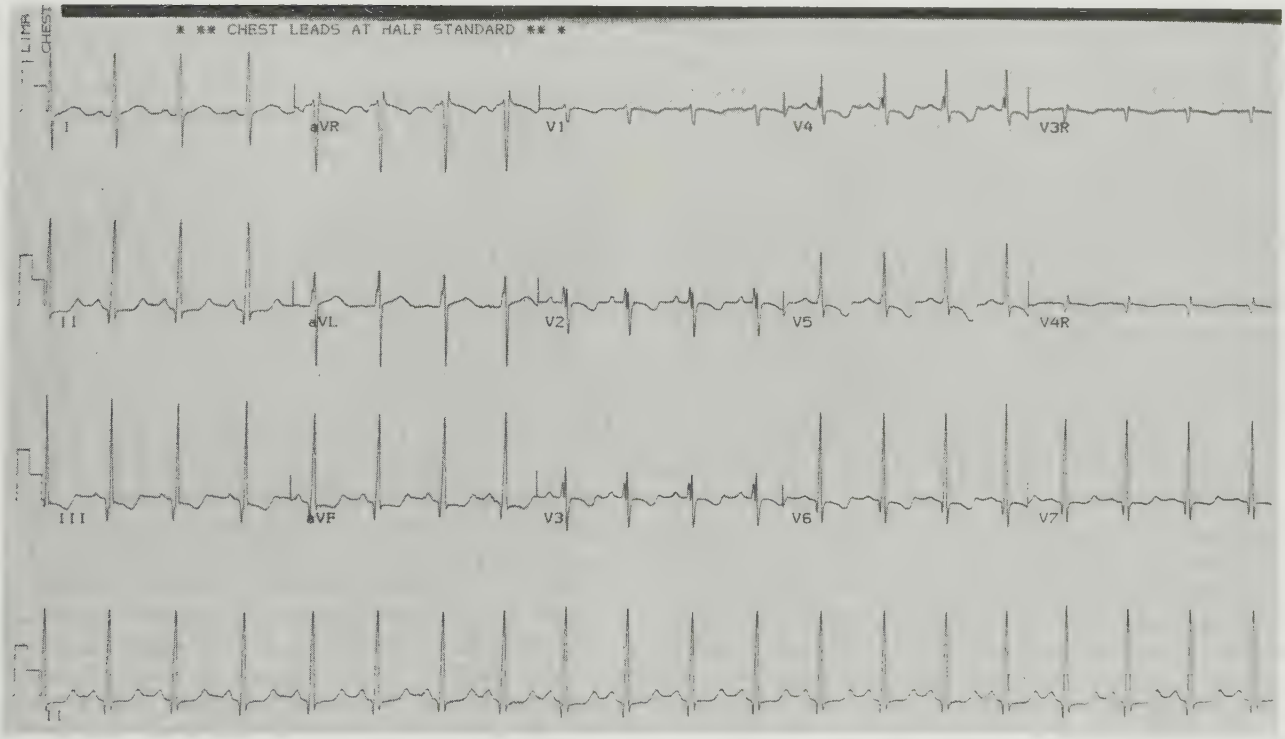

Fig. 80–15. Electrocardiogram (ECG) of a 9-month-old female with severe aortic coarctation. The tracing was interpreted to show left ventricular hypertrophy with left ventricular "strain" pattern. Note ½ std. chest leads. These ECG findings influenced decision for immediate surgery. Strain pattern was no longer present on postoperative tracing.

close the VSD in the same operation through a different incision; alternatively, the VSD may be closed several days later if the infant continues to require ventilator support. The 10 to 20% of infants in failure with coarctation who have isolated discrete obstruction will initially receive medical therapy and occasionally exhibit prompt and obvious improvement, in which case coarctation surgery is not performed. If poor feeding, poor weight gain, and respiratory difficulties are not reversed promptly, operation is offered. Coarctation repair is not offered electively to asymptomatic infants based on recognition of surgical risk and morbidity as well as knowledge that restenosis following repair in infancy is likely.

Unusual Coarctation

Less commonly identified forms of coarctation must be considered when a clinical diagnosis of coarctation of the aorta is made.[43] The usual isthmic narrowing just beyond the origin of the left subclavian artery can be accompanied by variations in related vessels such as patency of the ductus arteriosus, stenosis of the origin of the left subclavian artery, or anomalous origin of either left or right subclavian artery. In addition, coarctation can be found in an atypical location in the ascending aorta, transverse arch, distal thoracic aorta, or abdominal aorta. Extremely rare cases include the coexistence of multiple sites of coarctation and coarctation with right aortic arch and right descending aorta. Definitive diagnosis of one of these variations in anatomy depends on cardiac catheterization and angiography. Coarctation of the aorta proximal to the origin of both subclavian arteries invalidates the utility of arm and leg pulse differential in making the diagnosis of coarctation of the aorta.

Abdominal coarctation should be recognized in advance of surgery, so that the proper operative approach can be made. In contrast to the more common occurrence of thoracic coarctation in males, the abdominal site is more common in females. Clues to the presence of this alternate site of narrowing may be the presence of a murmur over the abdomen anteriorly and posteriorly as well as less obvious rib-notching which, when present, may be seen only at the borders of the lower rib owing to the limited possibility of development of collateral vessels in the abdomen. Historically, a patient may volunteer an important history of leg cramps with claudication. Abdominal coarctations are frequently longer in length and may involve the origin of the renal arteries or other abdominal aortic branches. Extreme cases of abdominal coarctation extend to and involve the origin of the femoral arteries (Fig. 80–14). Some authors have stated that abdominal coarctation is "always" acquired as part of an arteritis[44,45] which, when it affects the aortic arch and major vessels, has been referred to as "Takayasu's syndrome" or "pulseless disease."[46]

Histologically, Takayasu's arteritis is characterized by aortic segments that are narrowed by marked intimal hyperplasia and alternate with areas of aneurysm formation. The diffuse nature of the aortic involvement and the frequent association with a systemic illness similar to collagen vascular disease further typify this disease entity. The bizarre reversal of pulse discrepancy with obliterated upper extremity pulses and palpable femoral pulses and lower extremity hypertension, particularly when renal arteries are involved and femoral arteries are spared, is a curious presentation referred to by some as *reversed coarctation*. Whether isolated abdominal coarctation is ever a congenital anomaly or only exists as a post-inflammatory narrowing of the aortic lumen is not clear. But the progressive nature of this entity and its striking preponderance in females provides clinical overlap with recognizable Takayasu's disease.

Another condition, referred to as *pseudocoarctation*, is due to abnormal elongation and tortuosity of the aorta that does not result in sufficient narrowing of the lumen to allow measurement of an important gradient across the site of the kinking in the vessel.[47] This is further characterized by the lack of development of collateral vessels. Qualitatively, the medial ridge characteristic of true coarctation is present but its effect is slight. In a strict sense, pseudocoarctation and "kinking or buckling of the aorta" are probably forms of very mild coarctation. Occasionally, the appearance of pseudocoarctation may also be accompanied by a severe discrete coarctation. In these cases, a gradient at the site can be measured.

Multiple coarctation sites are rare. It is unfortunate when they are identified after repair of the coarctation in the usual site has not yielded relief of the gradient. Of interest is the recent recognition of the unusual occurrence of multiple coarctations (transverse arch as well as isthmic narrowings) in two Saudi infants, one with right aortic arch.

Functional coarctation may be produced by extrinsic pressure on the aorta by mediastinal masses or tumors. A dissecting thoracic aneurysm with involvement of the origin of the left subclavian artery may produce pulse discrepancy between the right and left arms. The rare spontaneous thrombosis of the aorta in the neonate may present like coarctation, resulting in a surgical emergency.[48] Disappearance of femoral pulses in the newborn may also be a complication of indwelling umbilical artery lines leading to thrombosis or vessel spasm.

NATURAL HISTORY AND COMPLICATIONS

The longterm prognosis of patients with unoperated coarctation of the aorta is primarily gleaned from autopsy studies rather than from longterm followup of patients with a clinical diagnosis of coarctation of the aorta.[13,60] According to these early reports, coarctation of the aorta was accompanied by a 90% mortality by age 50. The mean age of death was 35 years. Contributing to the cause of death were intracranial hemorrhage (11% of cases in autopsy series), aortic rupture or dissection (23%), endocarditis (22%), and congestive heart failure (18%).

The increased incidence of berry aneurysms in patients with aortic coarctation and the feared consequence of intracranial hemorrhage have been used to further support decisions for repair of aortic coarctation. Aneurysms of the circle of Willis (berry aneurysms) are thought to occur in up to 10% of patients with coarctation of the aorta. The likelihood of rupture appears to be greater in later years.[7] A review of cases of coarctation with death from cerebral aneurysm included its occurrence in the youngest case, a 13-year-old[62]; the average age at the time of death from intracranial hemorrhage was 28 years.[63] The observations that aneurysms were multiple in 4 of 11 patients and that the largest aneurysms were seen in older patients emphasizes the impression that longstanding hypertension promotes aneurysm growth.

There is evidence that the risk of intracranial hemorrhage correlates with the actual level of blood pressure; however, hypertension is not considered to be the sole causative factor. A congenital maldevelopment of the vessel wall predisposing to

aneurysm formation has been implicated. Mycotic aneurysms forming in the central nervous system, which in turn serve as the site for intracranial hemorrhage, are thought to be less common than the rupture of a congenital berry aneurysm. Following intracranial hemorrhage the likelihood of death is high, as is the risk of residual hemiplegia; however, there is also the potential for significant improvement in neurologic status, or even recovery.[63]

Cerebral aneurysm is usually silent until its rupture produces symptoms. When a ruptured aneurysm is found in a patient with aortic coarctation it is generally agreed that surgical treatment of both lesions will be necessary to try to alter the >75% probability of mortality. The timing and sequence of repair has been debated. Some authors favor initial treatment of the aneurysm, while others advocate that coarctation repair should take priority.[64]

Cerebral hemorrhage in neonates with coarctation of the aorta is extremely rare.[65] The late recognition of aortic coarctation in severely ill infants with previous cerebral hemorrhage may or may not be coincidental, as severe hypertension has not been documented prior to the hemorrhage. The management of an infant with coarctation and preexisting cerebral hemorrhage from whatever cause will complicate the decision regarding surgical therapy. It will be necessary to address whether emergency coarctation surgery is indicated or whether judicious repair of a mild or moderate coarctation will add additional risk and complicate recovery from antecedent (and possibly unrelated) cerebral injury.

Aortic rupture or dissection, as part of the natural history of coarctation of the aorta, is described as a cause of death in all large longterm natural history surveys of patients with coarctation of the aorta. In this lesion, rupture occurs in the thoracic aorta related to an intrinsic abnormality of the media complicated by hypertension compounding the usual stresses placed on the aortic wall. Aortic rupture in association with coarctation occurs at one of two sites. Approximately three fourths of the cases occur in the ascending aorta. Less often, aortic rupture occurs distal to the coarctation. The proximal rupture is more common in an older age group, after the third decade of life, and is associated with the same factors that predispose to dissecting aneurysms such as intimal "wear and tear," medial degenerative changes, or (less common) infection. Normal stresses imposed on the aortic wall are aggravated by elevated systolic blood pressure, explaining why aortic rupture is seen more often in the hypertensive patient with coarctation of the aorta. In a large series of patients under age 40 with dissecting aneurysms, approximately one third had coarctation of the aorta. With ascending aortic aneurysm death usually occurs from sudden hemopericardium caused by rupture of the aneurysm into the pericardial sac.

The obstetrical experience in unoperated coarctation of the aorta has found that aortic dissection or rupture during pregnancy is rare but is the main hazard of pregnancy in patients with coarctation. In these patients the rupture is generally found in the ascending aorta. Rupture occurs in the last trimester, during labor, or in the postpartum period. It is not agreed whether hormonal factors during pregnancy alter the biochemical composition or intrinsic structure of the aortic wall and thus predispose it to rupture[66] or whether a pre-existing medical necrosis of the wall is subjected to normal hemodynamic alterations of pregnancy, including hypertension, hypervolemia, and widened pulse pressure.[67] It is apparent, however, that there is a true increase in the incidence of dissecting aneurysm from coarctation during pregnancy.[68,69] It is not known whether early operative repair of coarctation of the aorta will protect against the development of irreversible structural changes in the aortic wall that in turn may predispose to rare aortic rupture during pregnancy.

Rupture of the distal aorta can also occur spontaneously and, unlike the more common proximal rupture, is seen more frequently in younger patients. Its occurrence is promoted by endocarditis at the site of the traumatic jet lesion that occurs on the wall of the aorta just beyond the coarctation. In fact, the role of infective arteritis as a causative mechanism is likely. The distal aortic site is also the location for traction aneurysms at the site of the ligamentum arteriosum, and the location for marked aneurysmal formation as part of post-stenotic dilation beyond the coarctation site. The hydrodynamic forces resulting from the jetting of blood through the coarctation site at high velocity have been implicated. With distal rupture, the aorta erodes into the left bronchus, esophagus, or left pleural cavity with rupture almost invariably sudden, dramatic, and fatal.

Endocarditis occurring with coarctation of the aorta is a cause of death that has been reduced through the years due to early recognition of the problem and improved antibiotic therapy.[63] The present projected incidence of 1.3% per year may in part be related to the additional liability of a bicuspid aortic valve. The infection is most likely to occur in the aorta just distal to the coarctation or on the bicuspid aortic valve. Confirmation of the site of infection is not always possible although improved recognition of vegetations with echocardiography may help. When aortic regurgitation becomes apparent during endocarditis, the aortic valve site is suspected. Endocarditis prophylaxis is recommended for use in all patients with coarctation of the aorta preoperatively as well as after surgical repair.

Congestive heart failure with coarctation of the aorta should raise the question of associated defects in infants as well as in those patients beyond the third or fourth decade of life when superimposed valvular heart disease, coronary artery disease, and renal disease become more likely. It does appear that the incidence of congestive heart failure increases with time and that left ventricular failure from longstanding hypertension is more evident after age 40.

The natural history of uncomplicated coarctation suggests that most patients can do quite well until early adulthood, when the risk of complications in association with unoperated coarctation begins to increase. In spite of the knowledge that systemic hypertension is a risk factor of coronary artery disease, myocardial infarction is not a major cause of death in patients with unoperated coarctation.[70] Theoretically, it is possible that adequate coronary flow is maintained by collateral circulation or an increase in the area of the coronary lumen. The morbidity and mortality from unoperated coarctation is high, prompting concern about interruption of the natural history of coarctation. Improvements in surgical therapy coupled with knowledge that prolonged preoperative hypertension and surgery after age 25 are associated with a risk of premature cardiovascular death have influenced pediatric cardiologists to consider that the optimal time for therapy of coarctation of the aorta is between ages 5 and 7.

THERAPY

The goal of therapy for all cases of coarctation is to offer a single definitive procedure at the time of lowest procedural risk

that in turn best affords long-term relief of hypertension. Medical management is justified when treatment of the patient will improve the risks and eventual outcome of surgery. Correction of coarctation of the aorta results only when relief of the mechanical obstruction is accomplished. Traditionally, this has been achieved by surgical therapy, although newer methods of dilation of the coarctation site by interventional catheterization are now available.

Medical Therapy

Medical treatment of patients with coarctation of the aorta is particularly applicable to the sick neonate presenting with severe congestive heart failure or shock. Prostaglandin infusion allows dilation of the ductus arteriosus and permits flow via the ductus beyond the coarctation.[71] Renal blood flow is enhanced, with reversal of hypoperfusion and shock; the goal is to make the infant a better candidate for surgery. Congestive heart failure is further improved by furosemide, with digoxin therapy added if ventricular function is assessed to be poor. Infants who have complicated coarctation are unlikely to respond to medical therapy alone, and the goal of treatment becomes that of stabilizing the patient in preparation for surgery. This management is based on a number of reports from several centers supporting a higher rate of survival with surgical treatment compared with medical treatment. There are staunch proponents of continued medical therapy alone for infants with isolated coarctation of the aorta based on the experience that a number of these infants will improve with time as collateral vessels develop over months of observation. With some of these children, medical therapy can be discontinued in late infancy or early childhood, allowing further growth of the child and surgical repair of the coarctation electively performed at school age. Others would recommend repair of isolated coarctation at any age if the patient is symptomatic.

Enthusiasm for medical treatment of coarctation hypertension with beta-adrenergic blockers or other antihypertensive agents is difficult to support if one believes that the upper body hypertension is a normal compensatory mechanism brought into play to overcome the resistance imposed by the obstructing coarctation. If the blood pressure elevation is so severe that it requires treatment by pharmacologic means, it seems likely that surgery should be performed.

Abdominal coarctation of the aorta may present special problems in that more severe hypertension is seen in this condition, particularly when there is associated renal artery involvement. Treatment of hypertension by medical means alone is usually impossible and can be dangerous, and an attempt at surgery is generally preferred. Treatment of residual hypertension, once surgery has been performed, may be a longterm compromise if no further surgical procedure would be beneficial.

Surgical Therapy

The earliest method of repair of coarctation in an experimental animal was reported by Blalock and Park in 1944, with acute experiments using the left subclavian or left carotid artery to bypass the created coarctation segment in an end-to-side manner.[72] A high incidence of postoperative paralysis was reported as a result of interference with arterial supply to the spinal cord.

Surgical correction of coarctation of the aorta in humans was first performed in October, 1944, by Drs. Crafoord and Nylin in Sweden[73] and in July, 1945, by Drs. Gross and Huffnagel in Boston.[74] These physicians demonstrated that in the presence of well-developed collaterals, the aorta could be safely cross-clamped just above and below the coarctation site, allowing removal of the coarcted area followed by re-approximation of the ends of the aorta. This operation, using resection and end-to-end anastomosis, remains the standard surgical form of therapy today in individuals with localized discrete obstruction. Overall operative mortality is highest (16.4%) in patients under 1 year of age, falling to 1.4% in patients 1 to 69 years of age.[75] The surgical approach is by way of a left posterolateral thoracotomy through the fourth left intercostal space using a curved incision extending from the anterior axillary line to the tip of the scapula. In children the ribs are spread to allow surgical access, whereas rib resection may be necessary in adults. If additional intracardiac repairs are necessary, the excision is extended across the sternum, with transection of the sternum, and both fourth intercostal spaces are entered. The patient is not usually placed on bypass since well-developed collaterals permit safe cross-clamping of the aorta. A ductus or ligamentum is usually divided to enhance mobility of the aorta. The best result, with the lowest chance of recoarctation, is thought to be gained when a continuous suture line is used posteriorly and completion anteriorly is done with interrupted absorbable vascular sutures to allow for growth of the anastomosis (Fig. 80–16).[76]

When the anatomy of the coarctation segment varies, alternative repair methods may be required (Fig. 80–17). Proponents of patch graft aortoplasty,[77] as first proposed by Vosschulte in 1957, believe it may be simpler to incise the area of coarctation longitudinally, resect the coarctation shelf, and insert an elliptical Dacron patch across the area allowing extension of the patch up onto the base of the left subclavian artery. Other techniques using interposition grafts and conduits placed in parallel to the descending aorta have been used in special circumstances, with stated advantages being that there is less mobilization of the aorta required, fewer injuries to the recurrent laryngeal nerve, and avoidance of a circular constricting anastomosis.

Due to a high rate of restenosis—up to 60% when resection and end-to-end anastomosis was used in infants[78]—Waldhausen and Nahrwold devised a repair using a flap of the subclavian artery.[79] In this operation the subclavian artery is ligated distally and a vascular pedicle is created from the subclavian, which is then used to bridge the hypoplastic segment. The vertebral artery must always be ligated to avoid subclavian steal.[80] Resultant mild discrepancy in limb length occurs after ligation of the subclavian, similar to that recognized after Blalock-Taussig shunts.[81]

Proponents of this method of repair are enthusiastic that the vascular subclavian flap as well as the posterior wall of the aorta will grow, and that the avoidance of a circumferential suture line is ideal.[58,82] Other surgeons report that restenosis with this method of repair is high (and perhaps "inevitable" when an infant under 8 weeks of age has subclavian flap repair because of involution of ductal tissue and perhaps the further growth of the coarctation shelf that is left behind).[83] The previous claims that the incidence of restenosis would be much lower than with resection and end-to-end techniques may not be true.[84,85] The subclavian flap procedure (Fig. 80–18) may be preferable in infants in whom the resection and end-to-end procedure will leave an unacceptably small anastomosis due to additional severe isthmic hypoplasia. No one method of repair is ideal for all patients. The best repair in a child would seem to circumvent the need for prosthetic materials

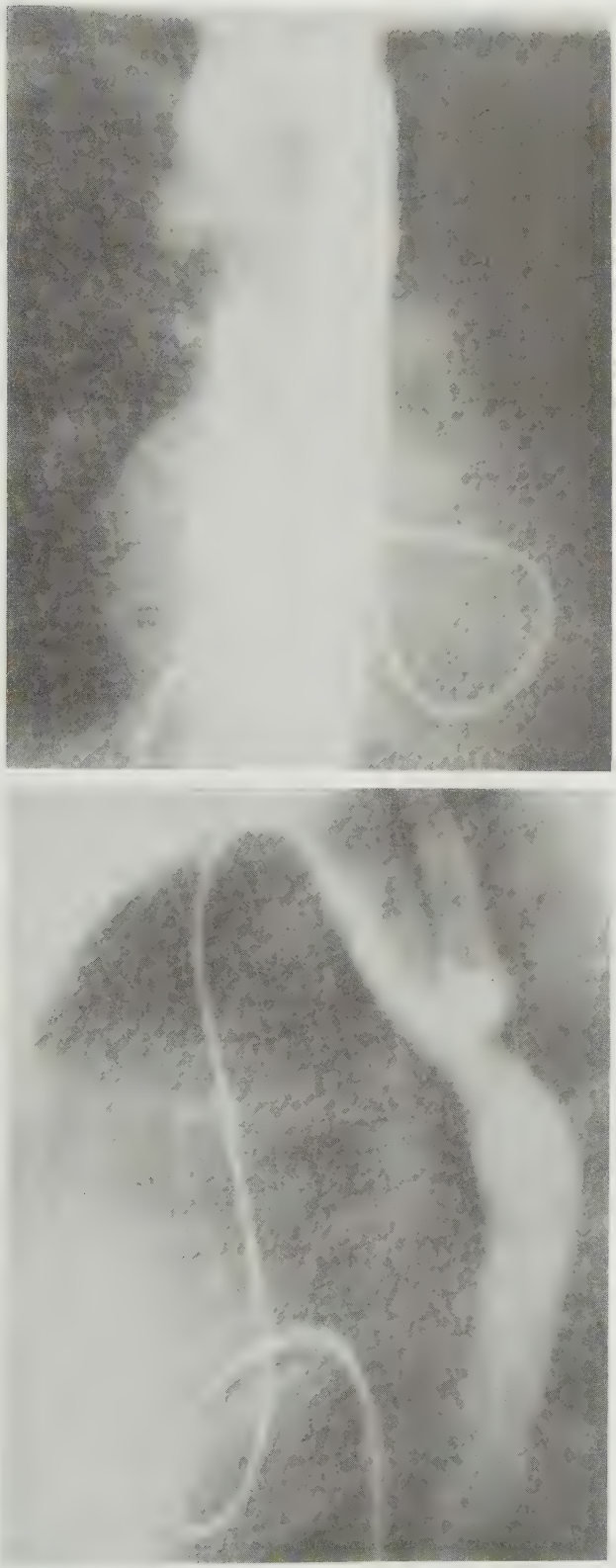

Fig. 80–16. Aortogram performed 23 years after repair of coarctation of the aorta by resection and end-to-end anastomosis in a 15-day-old female. The pressure measured proximal to the repair was 125/80 mm Hg, and 130/75 mm Hg distal to the repair on withdrawal tracing at catheterization.

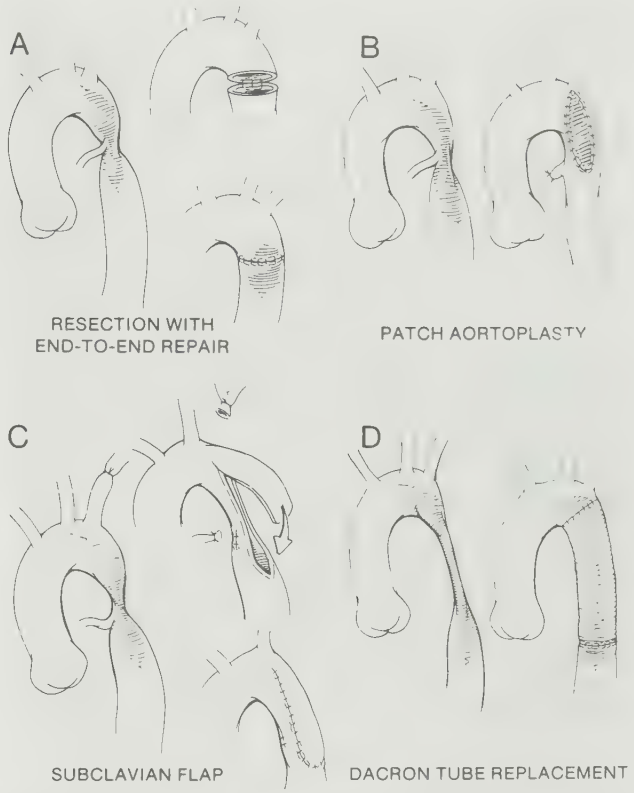

Fig. 80–17. A–D. Methods of surgical repair of aortic coarctation (see text).

and allow for growth of the surgical area. Residual gradients and need for reoperation are most often found when surgery is necessitated at a young age; the age seemingly has greater influence than the technique used.

Information on the normal growth of the aorta projects that the aortic diameter increases threefold from birth to maturity, with the most rapid change occurring in early childhood.[86] The diameter of the aorta at 3 years of age is 55% the diameter in adulthood. Physiologic evidence agrees with experimental data indicating that important obstruction to blood flow through a stenotic orifice occurs when the diameter is reduced by 50% or greater. Optimally, the earliest time that successful operation is expected is age 3 years, with provisions that the surgeon entirely excise the area of constriction and complete the end-to-end anastomosis without compromising lumen size by the circumferential anastomosis. At this age, even if the anastomosis did not grow, it would not result in more than a 50% stenosis and would not produce a gradient.

When surgery is offered, surgical judgment and experience in choosing a technique based on the anatomy encountered will offer the best relief of obstruction and least likelihood of recoarctation. The potential for restenosis exists unless the coarctation shelf lesion is completely removed as well as the encircling "ductal tissue," if present.

Intraoperative and Postoperative Complications

Important complications related to coarctation surgery are infrequent but include 1) recurrent laryngeal nerve injury; 2) phrenic nerve injury; 3) predisposition to bleeding both from collateral

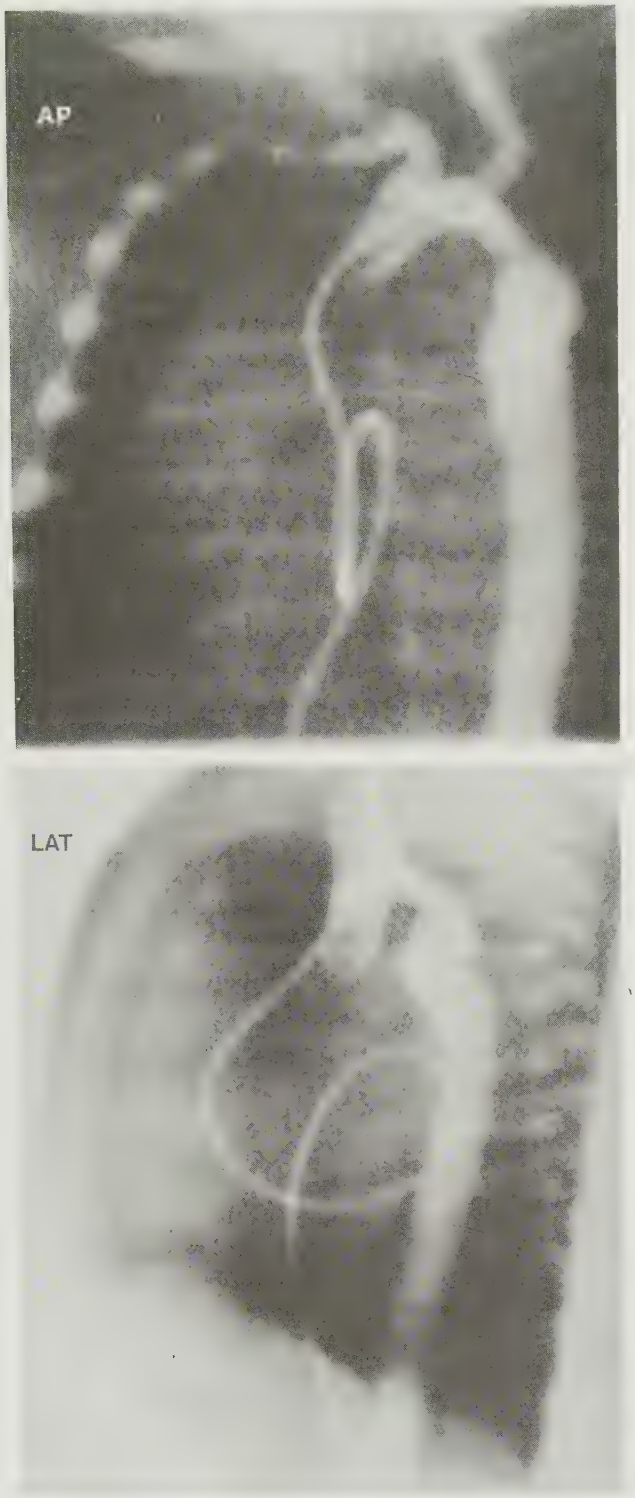

Fig. 80–18. Repair of aortic coarctation at age 4 days by subclavian flap technique. Aortic root angiogram performed 2 weeks postoperatively reveals patency of the repair with persistent hypoplasia of transverse arch. Infant has Taussig-Bing anomaly in addition to coarctation. Withdrawal pressures: ascending aorta 84/42 mm Hg, transverse arch 76/42 mm Hg, descending aorta 72/42 mm Hg.

vessels and from the high pressure aortic suture line; 4) chylothorax; 5) postcoarctectomy syndrome (mesenteric arteritis); 6) paradoxical postoperative hypertension; and 7) spinal cord ischemia.

Traction or electrocautery can injure the recurrent laryngeal nerve as it loops around the ductus or ligamentum before its ascent; this problem is manifest clinically as persistent hoarseness. Even less frequently, the phrenic nerve, located more anteriorly on the border of the pericardium, can be injured and result in unilateral diaphragmatic paralysis.

Bleeding from extensive chest wall collaterals or from the high pressure suture lines on the aorta is the most common postoperative problem following coarctation repair. Bleeding is lessened if preclotted synthetic materials are used for prosthetic reconstruction. Catastrophic disruption of the suture line with resultant hemorrhage has occurred early after subclavian flap repair and late, on another occasion, when postoperative endocarditis weakened the area of surgical repair.

Chylothorax may result from tearing or perforation of the thoracic duct, which, because it crosses behind the aortic arch and left subclavian artery,[87] is vulnerable during dissection. Nonoperative management of this complication with multiple thoracenteses, chest tube placement, and a diet of medium chain triglycerides is often effective; however, surgical treatment of this complication before caloric and protein losses are severe should be considered when chylous drainage persists. The fairly constant entry of the thoracic duct as it enters the thorax through the aortic hiatus in the diaphragm allows ligation, although reportedly 28% of individuals may have two or more major ducts at the level of the diaphragm.[88] The management of postoperative chylothorax is discussed in detail in Chapter 151.

A postoperative problem unique to coarctation repair is that of postcoarctectomy syndrome (mesenteric arteritis).[89,90] When forceful pulsatile flow is introduced postoperatively to vessels beyond the coarctation, thin walled arterioles overdistend and may rupture. Mesenteric vessels, poorly supported by surrounding tissue, are particularly at risk for damage. In addition, reflex arteriolar vasoconstriction occurs in distal vascular beds, contributing to postoperative hypertension. Clinical manifestations are abdominal pain, abdominal distention, vomiting, and decreased bowel sounds with progression to an "acute abdomen" when hemorrhage into the intestinal wall occurs. In severe cases, laparotomy may be required for treatment of bowel necrosis. This complication is thought to be more common if feedings are introduced early postoperatively. To avoid the development of this problem, nasogastric tubes are left in place for 48 hours postoperatively and the patient is continued NPO for at least 72 hours. Feeding is begun slowly with clear liquids with rapid progress to a full diet. Important systolic hypertension is treated as well as diastolic pressures in excess of 95 to 100 mm Hg, since hypertension appears to be an essential component of the syndrome.

The mechanism of postoperative rebound hypertension seen after successful repair of coarctation is partially explained on the basis of reflex vasospasm in the vascular beds distal to the coarctation[91,92] as well as a baroreceptor-mediated role for increased sympathetic activity. It is not unusual for blood pressure to return to or exceed preoperative levels and require treatment. Control of postoperative rebound hypertension may be important in decreasing the frequency of postcoarctectomy syndrome.[93]

The most feared consequence of surgery is paralysis of the lower extremities resulting from spinal cord injury. Fortunately, this is rarely reported. The incidence is less than 0.5% in more than 12,000 cases compiled in experience from several cardiovascular centers.[94] No one specific factor is implicated as causative in all cases where paralysis has resulted after surgery; however, the risk may be increased by prolonged aortic cross-clamping, reduced arterial collateral vessels, sacrifice of intercostal vessels during repair, or even hyperthermia.[95] A clue to the possible development of a serious problem is that when the aorta is cross-clamped, the proximal blood pressure rises dramatically and the distal aorta is observed to become nonpulsatile and collapsed. This is explained on the basis of poor development of a well-developed and protective collateral supply. It is possible that immediate recognition of this problem would allow removal of surgical clamps with reversibility of the brief neuronal ischemia resulting from circulatory failure. If collaterals are judged preoperatively to be inadequate, the need for surgery should be carefully reassessed. If surgery is required, further methods of cord protection could be employed, including hypothermia, cardiopulmonary bypass, or bypass graft repair with only partial aortic clamping. There is no definite rule about the number or location of intercostal vessels that can be safely sacrificed during coarctation repair. The best protection against neurologic sequelae from operation is thought to be the presence of a well-developed collateral circulation.

Surgical therapy remains the most definitive means of effecting relief of obstruction. Because of its role in managing coarctation of the aorta successfully for over 40 years, surgical intervention is the standard against which new treatments must be compared.

Therapy with Interventional Catheterization

Coarctation of the aorta can be successfully dilated with balloon angioplastic techniques (Fig. 80–19). The feasibility of relieving obstruction, particularly when discrete, has been reported from many centers.[96,97] This method of treatment is still controversial and requires comparison with surgical treatment. It is still not known whether recurrence rates for coarctation will be higher with dilation procedures or if other longterm complications will be a problem.

Originally, percutaneous transluminal angioplastic techniques were demonstrated to be effective in patients who had developed restenosis after previous coarctation surgery.[98] Recurrent coarctations appearing after surgical end-to-end anastomosis, patch angioplasty, and subclavian flap have been successfully dilated. It has been hypothesized that there is protection against rupture of the aorta resulting from postoperative scarring and fibrosis of the aortic wall. It is thought that, in spite of the higher inflation pressures required for dilation of restenosis lesions, vessel integrity will not be compromised. For successful angioplasty, the intima and part or all of the media is disrupted when the vessel diameter increases.[99] Although late healing may be complete, the potential for aneurysm formation immediately or in longterm followup has raised concern about this procedure. Unusually high rates of aneurysm formation reported by some centers may be further substantiated by others who are carefully following postangioplasty patients.[100] Aneurysm formation does not invariably occur, however, and its occurrence is rare on short-term prospective followup in our institution.[42] Furthermore, aneurysm after coarctation repair is also found in surgical series, as discussed later in this chapter.

The procedure is described in detail in Chapter 130. Briefly, the technique involves the retrograde insertion of a dilating catheter over a guide wire from a femoral or umbilical arterial approach. Concern for overdistention and rupture of the aorta have resulted in conservative calculations for the effective dilation diameter of the balloon. Inflated diameters should be 2½ times that of the diameter of the coarctation, or, the balloon should be 1 to 2 mm greater than the diameter of the aorta measured at the base of the left subclavian artery. The catheter is positioned in the aorta with the midpoint of the balloon at the narrowest site and the balloon is inflated with dilute radiopaque contrast medium for a few seconds to achieve elimination of the waste produced by the coarctation lesion. The actual dilation of the coarctation is painful and patients should receive appropriate preprocedural sedation. Effective reduction in pressure gradient across the coarctation site is immediately apparent, as is angiographic evidence of widening. In certain circumstances, the use of two angioplasty balloons is preferable.

As with other interventional techniques, the significant advantages of a shorter hospital stay (average of three compared with 10 days), cost containment, and psychologic and cosmetic avoidance of operation must be considered. Postprocedural problems with paradoxical hypertension and/or postcoarctectomy syndrome are reportedly rare.[42,101] These considerations are less important if benefits of angioplasty are incomplete and further surgery is required. If treatment of coarctation of the aorta by dilation procedures results in weakening of the aortic wall with aneurysm formation and an increased longterm potential for rupture, traumatic injury to the aorta that promotes accelerated atheroma formation, or other unrecognized problems, then surgical treatment will continue to be a better longterm answer for these patients. The risk of injury to the femoral arteries also needs to be addressed. A particular concern has been raised relevant to the case with successful relief of coarctation gradient and an aneurysm resulting from the procedure that requires resection. In this setting, collateral vessels might have regressed, eliminating their protective effect during aortic cross-clamping; thus an operative technique may have to be used that includes methods for perfusing the lower body.

In spite of unanswered concern about the longterm effectiveness and margin of safety of treatment with coarctation dilation, there are circumstances wherein this treatment may be offered or preferred. If thoracotomy is considered especially high risk because of previous surgery, bleeding diathesis, associated medical conditions (for example, ruptured cerebral aneurysm), or perhaps in patients who place restrictions on the use of blood products, dilation may be a safer technique. The use of dilation procedures in infants is not clearly established, but when performed early, the approach can be from the umbilical route, sparing trauma to femoral vessels.[54,55] It is possible that this technique will offer enough palliation of infants who have severe left ventricular dysfunction in association with coarctation to allow postponement of surgery. Concerns from autopsy studies of patients with large areas of ductal tissue in the area of constriction project that balloon angioplasty will palliate only temporarily and that restenosis is inevitable.[102]

The availability of dilation techniques will prompt further followup of all patients with coarctation to compare treatment options. At this point the challenge to proponents of dilation pro-

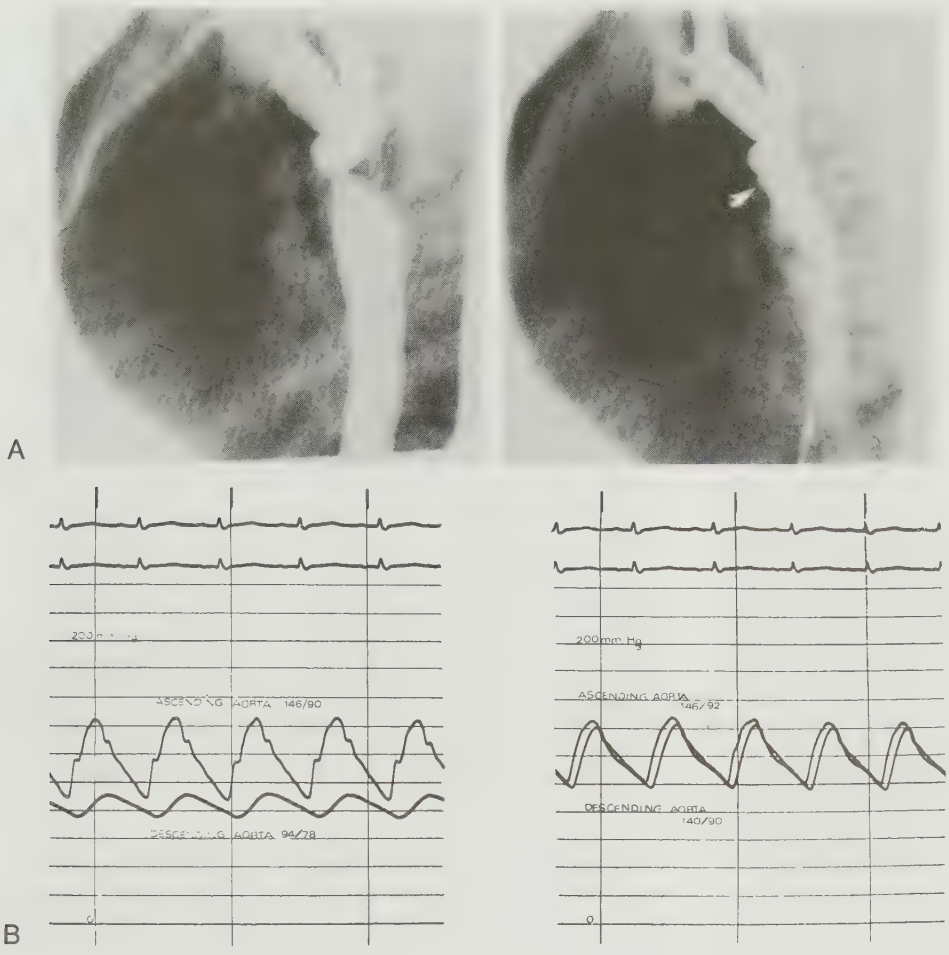

Fig. 80–19. Coarctation of aorta in a 5-year-old boy. A. Lateral angiogram prior to balloon angioplasty of aortic coarctation (left) and immediately following balloon angioplasty (right). Significant widening of the coarctation area has resulted, with minimal disruption of intima (arrow). B. Pressure tracings simultaneously recorded from ascending aorta and descending aorta prior to balloon dilation (left) and following dilation (right). The preprocedural peak gradient (52 mm Hg) was reduced to 6 mm Hg after dilation.

cedures for coarctation of the aorta is less proof of feasibility than longterm efficacy and safety of the technique.[103]

Postoperative Followup and Outcome

Natural history studies of coarctation confirm the high risk of mortality in infants as well as the shortened life expectancy for adults with isolated coarctation. With the availability of surgery, coarctation is now considered to be a defect that can and should be treated by operation. The likelihood of surgical success is dependent foremost on the age and size of the patient when operation is performed although the anatomy and technique of repair may also influence the outcome. Most pediatric cardiologists recommend elective correction of coarctation for all patients beyond the age of 3 years but before 10, despite lack of symptoms or severe upper extremity hypertension. Infants with a ventricular septal defect and coarctation who required pulmonary artery banding at the time of initial coarctation repair may have pulmonary debanding and ventricular septal defect closure in childhood with reoperation for coarctation postponed until adolescence. When surgery is offered beyond age 1 year, repair should consist of resection and end-to-end anastomosis unless unfavorable anatomy dictates an alternate method of repair. The application of subclavian flap techniques in young infants is enthusiastically supported at this time, although the claims of significantly lower incidence of restenosis have not been as fully evaluated as the resection and end-to-end technique. Long-term results of resection versus patch aortoplasty repair for coarctation are comparable in some centers.[104] In evaluating the longterm results, the distinction needs to be made between poor relief of obstruction and recoarctation or lack of growth of the anastomotic site.[105]

Long-term followup of all patients with coarctation of the aorta is mandatory. Aortic aneurysms are a long-term sequela of repairs using patch graft and tubular graft technique.[106] The aneurysms are thought to result because of the change in tensile strength rendered to the circumference of the vessel.[107,108] When these techniques are used, selection of patch material may play a role. In general, a patch graft aneurysm is found on the aortic wall opposite the patch graft. This situation occurs because the patch is less elastic than the aortic wall and the pulse wave is transmitted to the aorta opposite the graft. False aneurysms have formed at suture lines following partial disruption, with infection having a contributory role in some instances. Structural weakness in the arterial wall due to atherosclerosis may also be important in causation. The differences in reported frequency of postoperative aneurysms vary with the length of followup and awareness of the problem. The incidence estimated by one group using patch angioplasty repair is as high as 38% by 14 years postoperatively.[109] Often, followup roentgenographic studies will provide a clue to aneurysm formation. A rare presentation with development of hoarseness from compression of the recurrent laryngeal nerve has also been found. Aneurysm formation after patch angioplasty in children is recognized, thus, advanced age is not a necessary factor.[110]

Some surgeons, because of the concern about vessel rupture, aggressively approach aneurysms developing after dilation tech-

niques. In other institutions, these aneurysms are observed without reoperation, based on the conjecture that the aortic wall may heal enough to make rupture unlikely. Operation for removal of an aneurysm is hazardous since the previous complete or excellent relief of the obstruction has encouraged regression of collateral flow. Cross-clamping of the aorta without perfusion techniques to protect the spinal cord might no longer be safe. Femoral–femoral bypass is often instituted in this situation.

Suggestions of improved survival and a lower incidence of subsequent coronary heart disease and cardiovascular events if surgery is performed at a younger age have prompted elective repair in childhood. This practice is further supported by findings that the period and degree of preoperative hypertension has some influence on whether hypertension will recur on followup or be poorly relieved by operation.[70,111] These considerations, as well as projections about normal growth of the aorta, have prompted pediatric cardiologists to recommend elective repair beyond 3 years of age but under 10 years of age.

Persistent hypertension after surgery is usually related to insufficient anastomosis width. This may be apparent soon postoperatively, with incomplete relief of obstruction, or much later, with "recoarctation" or failure of growth at the site of repair. Persistent hypertension independent of a residual pressure gradient may not, in fact, be greater in the population with operated coarctation when compared with the incidence of essential hypertension in the general population.[61,112] Adjunctive information obtained from exercise stress testing has been valuable in assessing some patients after coarctation repair.[113,114] Proponents of this testing feel that exercise augments any residual systolic gradient at the coarctation repair site and therefore is a more sensitive indicator of residual obstruction.

The belief that the incidence of calcific aortic stenosis as a late occurrence is low in patients with bicuspid aortic valve in association with coarctation has been emphasized by several authors.[112,115,116] It has been stated that initially insignificant aortic valve disease, without an aortic valve gradient at the time of coarctation repair, usually does not progress. Congenital aortic stenosis with coarctation is well recognized. On the other hand, late calcific changes in the bicuspid valve not documented to be stenotic at the time of coarctation repair are rare. A patient known to us had coarctation repair at age 13; no gradient was measured at the time of preoperative catheterization but bicuspid aortic valve was recognized. Severe calcific aortic stenosis with a 90 mm Hg gradient at catheterization necessitated valve replacement at age 29. The recent observations that an "equally bicuspid" aortic valve is the type seen more often in association with coarctation leads to the conjecture that a lower incidence of calcific change may be related to a less turbulent flow pattern.

The lifetime threat of endocarditis is addressed with continual use of antibiotic prophylaxis for dental and surgical manipulations. Insurability of patients with coarctation of the aorta is best in the group who have had a good result from operation. If postoperative patients are asymptomatic, are normotensive, and have gradients between arm and left cuff pressures of less than 10 mm Hg, they may obtain life insurance at standard rates from most large companies, although they may be required to pay more than standard rates.[117] Employment opportunities based on individual capabilities should not be dissimilar from those of peer groups. Assistance from cardiologists may be required in clarifying these concerns on an individual basis. Attention to residual coarctation may qualify patients for insurance when reoperation or dilation techniques are successfully performed.

Recommendations for the obstetrical management of the patient with coarctation of the aorta will vary; generalization is not possible.[118] In the patient who has had successful repair of coarctation, pregnancy may be anticipated to proceed without difficulty. Careful monitoring of blood pressure and use of antibiotic prophylaxis would seem prudent. It is possible that an individual patient may have aortitis or cystic medial necrosis complicating coarctation, which will persist even after successful repair,[119] so that pregnancy risks are still not completely defined. The recurrence risk of coarctation in offspring is low, in the range of 3%.

SUMMARY

Coarctation of the aorta is generally placed on the list of congenital cardiac defects that can be cured by surgery. Nevertheless, all patients require lifetime followup,[120,121] as one or more of the following problems may ultimately develop: 1) infective endocarditis, 2) calcific aortic stenosis, 3) aortic regurgitation, 4) mitral valve dysfunction, 5) systemic hypertension, 6) restenosis at coarctation site, 7) aneurysm of the aorta, either at the site of previous procedure or a "spontaneous dissection," 8) cerebrovascular accident, 9) complication of pregnancy, and 10) premature atherosclerotic cardiovascular disease.

A longer duration of preoperative hypertension has been observed to contribute to the risk of many of these complications. Optimistically, isolated coarctation when repaired successfully past the age of 3 years should allow for sufficient width of the anastomosis and permit normalization of blood pressure. It is hoped that the longterm followup of these younger patients will demonstrate that complications described in the unoperated natural history of coarctation can be eliminated by appropriately timed correction of the anomaly.

INTERRUPTION OF THE AORTIC ARCH

Interruption of the aortic arch is a congenital anomaly in which complete discontinuity exists between the ascending and the descending aorta in some location (Fig. 80–20).[122–125] When the aorta is represented by a cord of tissue without patency or when the lumen is completely obstructed without discontinuity of the vessel, the term *atretic segment* should be used. Interrupted aortic arch occurring as an isolated defect is rare. In interrupted aortic arch the descending aorta is almost always connected to the pulmonary artery by way of a patent ductus arteriosus. A VSD is usually present. In fact, the association of interrupted aortic arch, VSD, and ductus arteriosus is the usual situation. Interrupted aortic arch represents less than 1% of all congenital heart anomalies. The condition is usually fatal in infancy if untreated. Aggressive intervention has improved the potential for survival and possible favorable outcome.

ANATOMY

The site of interruption has important implications from a diagnostic as well as a surgical standpoint. The most familiar classification used is that of Celoria and Patton, based on the site of interruption with respect to the origin of the major branches from the aortic arch.[126] As schematically illustrated in Figure 80–21, type A interruption occurs distal to the left subclavian artery. Type

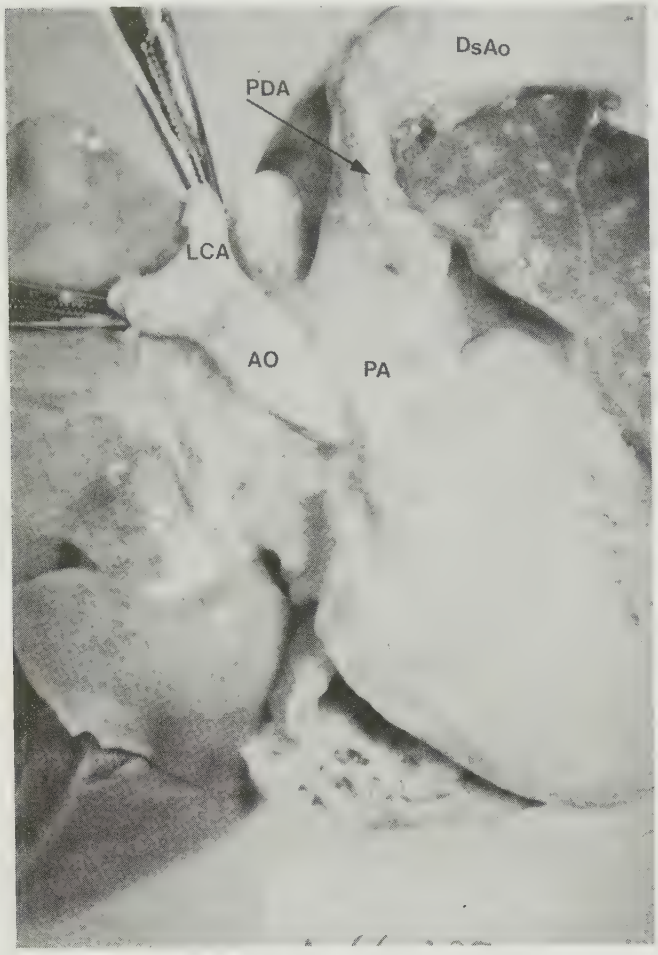

Fig. 80–20. Interrupted aortic arch, type B. Gross specimen. There is complete discontinuity in the aorta (AO) occurring just beyond the origin of the left carotid artery (LCA). The ductus (PDA) courses from the main pulmonary artery (PA) to supply the descending aorta (DsAo).

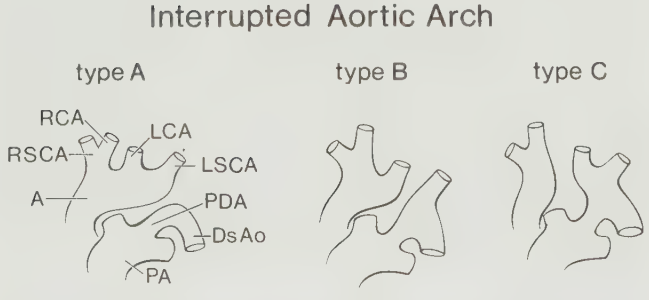

Fig. 80–21. Classification of interrupted aortic arch (with left aortic arch). Type A: Interruption distal to left subclavian artery (LSCA). Type B: Interruption between left carotid artery (LCA) and LSCA. Type C: Interruption between right innominate artery and LCA. A = aorta; RSCA = right subclavian artery; RCA = right carotid artery; PDA = patent ductus arteriosus; PA = pulmonary artery; DsAo = descending aorta: Right innominate branches RSCA and RCA are illustrated.

B refers to interruption between the left subclavian and the left carotid arteries. Type C interruption is present when there is a lack of continuity in the aorta between the right and left carotid arteries. Type B is the most commonly occurring form (approximately 53% of cases). Type A is present in 43% of cases, and type C in 4%. To our knowledge, interruption distal to the entry of the ductus has not been described. A VSD coexists in approximately 50% of patients with type A interruption and more than 80% of patients with type B interruption.[127] The high occurrence of an unusual type of VSD seen with type B interruption deserves emphasis.[128] The VSD is commonly a muscular outlet defect associated with malalignment of the trabecular and infundibular septum. Posterior deviation of the infundibular septum provides the substrate for subaortic obstruction, which may not be manifest until VSD closure has been accomplished (Fig. 80–22A).

Interrupted aortic arch is found with greater than expected frequency in conjunction with conotruncal abnormalities (including truncus arteriosus), and origin of both great vessels from the right ventricle with subpulmonary VSD (Taussig-Bing complex).[123,129] Less frequent associations are with aorticopulmonary window, single ventricle with transposition, and endocardial cushion defect with Down syndrome. Bicuspid aortic valve and narrowing of the subaortic outflow area as well as other potential left heart obstructive lesions, including mitral valve atresia or stenosis, should be sought in evaluation of a patient with aortic arch interruption. It is extremely rare for interrupted aortic arch to be present without a ductus arteriosus or other abnormality.

EMBRYOLOGY

The usual embryologic explanation for interruption of the aortic arch focuses on maldevelopment of the aortic arch system with early failure of formation or later regression of specific segments.[126,130] There are proponents of other, more basic, mechanisms based on altered intrauterine flow dynamics. These latter theories implicate patterns of decreased prograde aortic flow resulting in hypoplasia of the ascending aorta and regression or atrophy of "unused" aortic segments. A brief review of the development of the aortic arch system will make it conceptually easier to understand the embryologic events that might result in the repeated patterns of interruption (Fig. 80–23). With normal fetal development, blood flow to the head and upper extremities is separated at the level of the ductus from blood flow to the trunk and lower extremities. Type A interruption occurs when the discontinuity is in the segment of dorsal aorta between the fourth arch and the insertion of the ductal portion of the sixth arch. The migration of the left subclavian artery upward has occurred and its final position proximal to the site of interruption in type A interruption suggests an intrauterine event after the seventh week of gestation. With type A interruption, the head, neck, and upper extremities are supplied from the arch branches, with the distal aorta supplied from the pulmonary artery by way of right-to-left flow in the ductus arteriosus. With this site of involution distal to the subclavian artery and proximal to the ductus, the isthmus of the aorta is uniquely absent. Van Mierop and Kutsche have described how type A interruption and infantile coarctation are closely related, prenatally acquired lesions and contrast in several ways with type B interruption.[127]

Type B interruption occurs when there is involution or failure

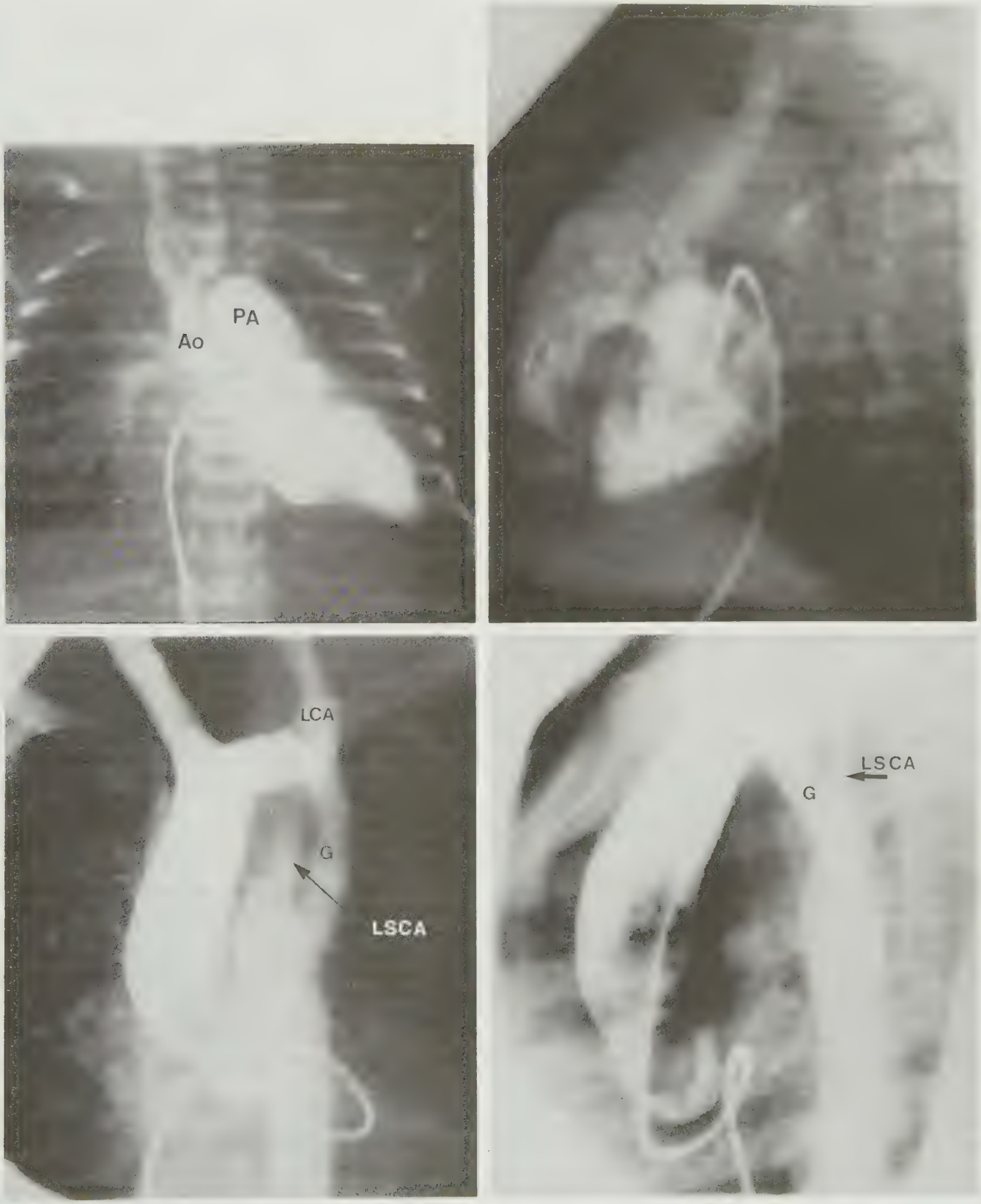

Fig. 80–22. (A) Interrupted aortic arch in a 3-day-old infant. AP (left) and LAT (right) angiogram-LV injection. Findings of markedly dilated pulmonary artery (PA) compared to small ascending aorta (Ao). The Ao appears to end just beyond the origin of the second branch, the left carotid artery (type B interruption). The ventricular septal defect (VSD) is outlined on the lateral frame with subaortic narrowing suggested due to deviation of infundibular septum (see text). (B) Interrupted aortic arch, type B. AP (left), LAT (right) angiographic frames. Six years after reconstruction with interposed 8 mm Gore-tex graft (G) placed between transverse aortic arch (at origin of left carotid artery [LCA]) and descending aorta. The left subclavian artery (LSCA) originally arose from the descending aorta beyond the interruption. Ascending aortic pressure is 100/60 mm Hg, femoral artery pressure 95/60 mm Hg.

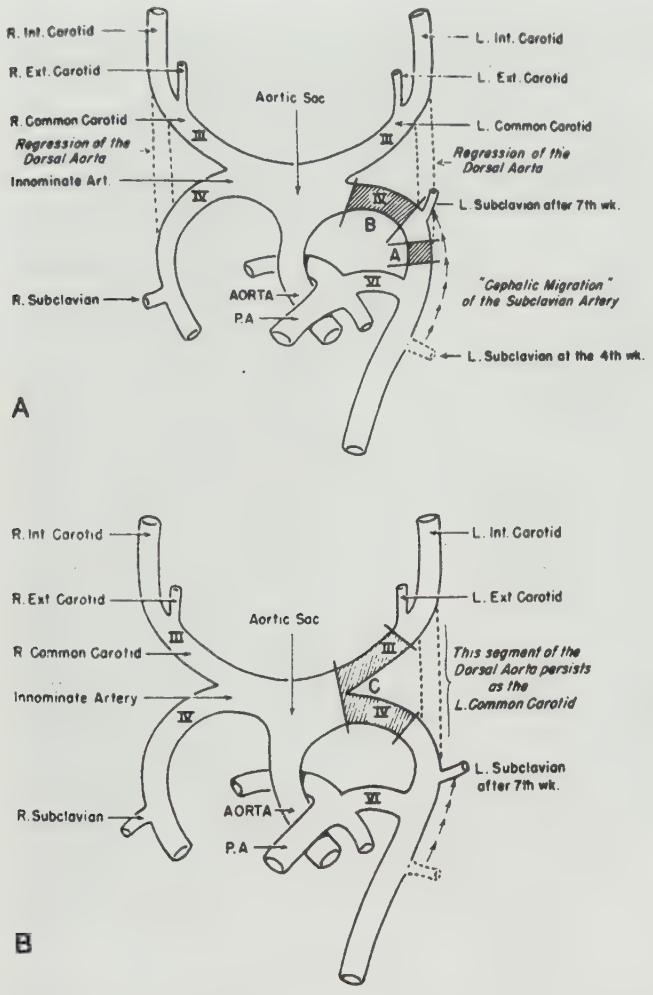

Fig. 80–23. (A) Schematic representation of primitive aortic arches from which great arteries are derived. Sites of aortic arch interruption, types A and B, are indicated. (B) Site of type C interruption. (Figure reproduced with permission from the American Heart Journal and Celoria, G.C., and Patton, R.B.: Congenital absence of the aortic arch. Am. Heart J., *58*:407, 1959.)

of formation of the left fourth arch as well as that segment of dorsal aorta between the fourth and sixth arches. Its occurrence must be prior to the seventh week of gestation, when the subclavian artery would have normally ascended. The subclavian artery arising below the interruption from the superior portion of the descending aorta, is supplied in the same manner as the lower body, by way of the ductal flow from the pulmonary artery.

The explanation for development of type C interruption distal to the innominate vessel is less clear (Fig. 80–23B). Two theories have been proposed. The first implicates complete failure of development of the left third and fourth arches, which would be replaced by persistence of the segment of dorsal aorta (earlier present between these arches) forming the left carotid artery. Seemingly more plausible is a second theory outlining failure of the left portion of the aortic sac to communicate with the third and fourth arches, allowing fusion of the left third and fourth arches to form the left carotid artery.

Proponents of the flow theory for intrauterine development of interrupted aortic arch outline the frequency with which the associated congenital defects serve to divert flow from the ascending aorta and increase flow by way of the pulmonary artery and ductus.[23] The unusual malalignment subpulmonary VSD and the leftward shift of the infundibular septum, producing narrowing of the left ventricular outflow tract above the level of the VSD, contribute to increased pulmonary flow at the expense of decreased aortic flow. This theory is further supported when transposition of the great arteries, VSD, and interrupted arch coexist as the role of rightward shift of the crista is recognized. Although the great majority of cases of interrupted aortic arch occur with intracardiac defects that cause reduced antegrade flow to the aorta, this does not explain every case. During fetal life, the circulatory burden imposed by interrupted aortic arch is slight since hemodynamics of right-to-left ductal shunting are the norm for all fetuses.

Even more embryologically complex is the association of interrupted aortic arch and third and fourth pharyngeal pouch defects, including absence of the thymus and parathyroid glands.[127] The term *DiGeorge syndrome* encompasses the immune defect resulting from thymic aplasia, with hypocalcemia as a result of parathyroid agenesis, and includes a striking frequency of type B interrupted arch, which occurs in at least 30% of cases. Conversely, 68% of patients with interrupted arch type B had DiGeorge's syndrome. Forms of aortic arch interruption other than type B exist with DiGeorge syndrome but are rare. The physical appearance of these children is distinct. An abnormal karyotype has been identified in some patients, characterized by partial monosomy of chromosome 22.[132,133] Immunologic abnormalities may be less severe in partial DiGeorge's syndrome, with hypoplasia rather than absence of thymic tissue, though here too a high association with aortic arch anomalies is present.[134] It is prudent to recommend investigation of the immune status and the serum calcium level of patients with known type B interruption and to assess parathyroid function. If urgent surgery is needed prior to investigations confirming the full spectrum of DiGeorge's syndrome, irradiated blood should be used to avoid graft-versus-host reaction. DiGeorge syndrome is addressed in further detail in Chapters 144 and 150.

PHYSIOLOGY

Interrupted aortic arch associated with ductus arteriosus is one of several malformations in which flow through the ductus arteriosus is uniformly reversed. Signs of heart failure usually occur in the early newborn period and deterioration is often rapid. As the ductus constricts, more blood is forced into the lungs, causing pulmonary edema, and less blood enters the descending aorta, resulting in low cardiac output with poor perfusion, shock, metabolic acidosis, and renal failure. Associated defects may create other alterations in blood flow patterns and other life-threatening sequelae.

CLINICAL FEATURES

Infants generally appear well at birth with pulses equal in all extremities in the presence of a widely patent ductus arteriosus with right-to-left flow. Infants can become critically ill and moribund rapidly with ductal closure. The lesion is characterized by early onset of symptoms and death from congestive heart failure

in the first days or weeks of life. Associated lesions may dominate the clinical picture. Differential cyanosis resulting from reversal of flow through the ductus arteriosus is the exception rather than the rule. This finding can be explained by the presence of the VSD allowing left-to-right shunting at the ventricular level so that the pulmonary artery saturation approaches that in the ascending aorta to the extent that upper body and lower body saturations are similar. A saturation difference of at least 10 to 15% must exist before differential cyanosis can be recognized clinically. Measurable differences in oxygen content can be found in spite of clinically inapparent differential cyanosis. When the ductus is widely patent, little or no blood pressure gradient may be measurable between the right upper extremity and lower extremity (Fig. 80–24). With constriction of the ductus, the expected pulse differential should be sought. It can be difficult to note a pulse difference when cardiovascular shock supervenes. A murmur is usually present in older children when subvalvular aortic stenosis or aortic stenosis coexists. No murmur is generated by the right-to-left ductus when widely patent. The VSD is usually nonrestrictive and not the source of a murmur. If a murmur and thrill are present, these are suggestive of additional defects. Ventricular arrhythmias have further complicated the course of some of these ill infants. The role of ductal dilation with prostaglandins is now a valuable adjunct to clinical management in conjunction with the more standard treatment for congestive failure and pulmonary edema.[71]

The chest roentgenogram almost invariably shows cardiac dilation and pulmonary congestion, neither of which is specific for this entity. Absence of the thymus may be suspected when the mediastinum is narrow. The ECG may be normal or may display right ventricular hypertrophy, left ventricular hypertrophy, or biventricular hypertrophy. The hypocalcemia accompanying aortic arch interruption with DiGeorge's syndrome prolongs the corrected QT interval. Echocardiography in the hands of an experienced operator has the potential to provide accurate noninvasive diagnosis of aortic arch interruption, but this is not an easy malformation to diagnose with echocardiography.[120] It is striking that the absence of the thymus gland makes imaging more difficult, because the presence of the thymus enhances technical aspects of recording. It is easy to recognize a discrepancy between the size of the great vessels with a small aorta and a large pulmonary artery. A ductus can be visualized continuing uninterrupted from the pulmonary artery to the descending aorta. From the suprasternal notch the ascending aorta has a straight course to the brachiocephalic vessels. In the most common type B form the aorta appears to end at the left common carotid artery with no suggestion of a transverse arch. One must be careful not to mistake the continuation of the main pulmonary artery, ductus, and descending aorta for a normal aortic arch. Further recognition of a malalignment VSD (visible on the long-axis view) and displacement of the infundibular septum with subaortic narrowing are often identified. The echocardiogram is also useful in assessing prostaglandin therapy for ductal dilation. The use of echocardiography for preoperative diagnosis without further angiography is being explored based on the confident diagnosis of interrupted aortic arch by a skilled examiner. The option for omitting catheterization in an extremely ill infant with poor renal function, thus eliminating the need for contrast material, expands the benefit of accurate noninvasive diagnosis.

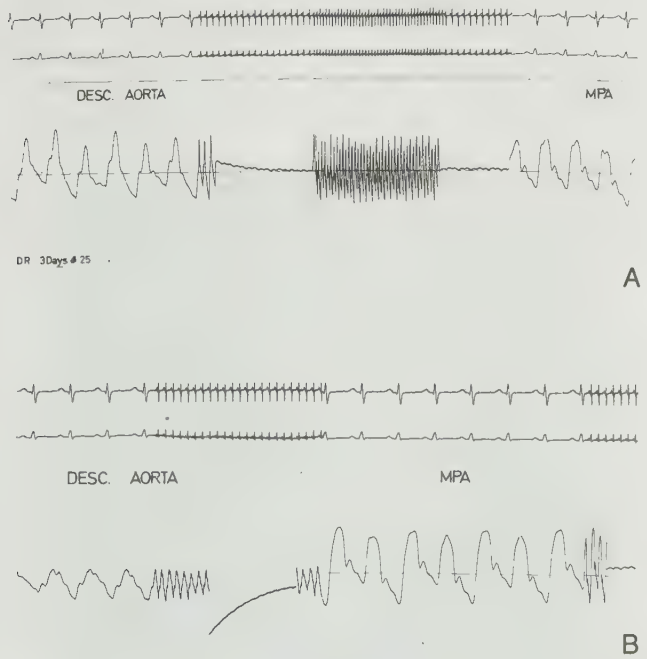

Fig. 80–24. Interrupted aortic arch-effect of prostaglandin E_1 (PGE_1) infusion on ductal patency (see text). Pressure recordings during catheterization. (A) Withdrawal pressure from descending aorta (DESC. AORTA) to main pulmonary artery (MPA) during PGE_1 infusion with ductus widely patent and no pressure gradient between the great vessels. (B) PGE_1 infusion stopped. Ductal constriction has occurred and there is a decrease in pressure in the descending aorta with a significant increase in MPA pressure as well as the pressure gradient between MPA and descending aorta.

CATHETERIZATION AND ANGIOGRAPHY

Catheterization is usually undertaken with the correct clinical impression including knowledge of the associated VSD and PDA. The infant is stabilized medically before catheterization. It is difficult to overemphasize the advantages gained with the use of prostaglandin therapy. In carrying out the procedure, it is important to enter all four heart chambers and the great vessels. If it is difficult to enter the aorta prograde across the VSD, the left ventricle can be entered by way of the mitral valve with a balloon catheter which is then inflated and floated into the ascending aorta. A catheter passed out the pulmonary artery generally passes preferentially across the ductus to the descending aorta. This latter catheter course does not distinguish aortic arch interruption from severe coarctation or widely patent ductus arteriosus in association with other defects. A catheter inserted in the umbilical artery cannot be passed retrograde around the arch, entering instead via a patent ductus and the pulmonary artery. Ventricular injections reveal hypoplasia of the aorta compared with the dilation of the pulmonary artery (Fig. 80–22A). It should be recognized that even large injections of contrast material delivered rapidly into a ventricle may fail to give accurate delineation of aortic arch anatomy. Best visualization of the detailed anatomy of interrupted aortic arch is obtained by injection directly into the ascending aorta. It is impossible to distinguish complete interruption from atresia of the aorta, in which a fibrous band connects the ascending and descending aortas. This distinction is not of practical value con-

sidering that the surgical approach would be the same. One may choose to employ catheterization primarily for detailed examination of the morphology of the aortic arch in a critically ill newborn and rely on echocardiographic definition of the VSD to avoid additional injections. When the decision is made to accompany repair of the interrupted aortic arch with pulmonary artery banding, the additional characterization of the VSD with angled angiographic injections can be postponed until a later catheterization. If the VSD is to be repaired at the same operation, complete characterization of the VSD will be necessary. Prostaglandin infusion should be carefully maintained during catheterization and surgery, to lessen the risks of these procedures.

NATURAL HISTORY

Patients with interruption of the aortic arch usually die early in infancy.[122] Only recently has this high mortality been improved with early recognition and prompt institution of prostaglandin therapy allowing stabilization of the infant to an extent where surgical therapy can be performed under favorable conditions. Long-term followup is not available in most instances, but the present survival of patients to midchildhood is encouraging. The additional burden of possible immune disorders and other serious birth defects correlated with DiGeorge's syndrome may pose more difficult problems than the congenital heart defect.

THERAPY

Medical therapy is rapidly instituted when a patient is thought to have interrupted aortic arch; it consists of prostaglandin infusion to dilate the ductus arteriosus and maintain perfusion to the lower body. Metabolic acidosis is treated, and its reversal can be achieved with bicarbonate as well as by improving perfusion. Improved pulses, reversal of anuria, and correction of acidosis can be dramatic when prostaglandin infusion is begun. Immediate therapy also involves correction of hypocalcemia as well as the anticipation of possible immune disorders by using only irradiated blood to prevent graft-versus-host disease if the possibility of DiGeorge's syndrome is entertained before confirmation is available. Pulmonary edema is treated with diuretic therapy and positive pressure ventilation. Digoxin therapy is reserved for patients who have demonstrably poor ventricular contractility on echocardiogram. Treatment of ventricular tachycardia has been required in some patients with simultaneous attempts to correct electrolyte abnormalities and metabolic acidosis.

Surgical Therapy

The goal of surgery is to restore continuity between the ascending and descending aorta by one of several techniques. The principal limitation to surgical outcome is the condition of the patient at the time of operation. Many centers limit the initial surgery to restoration of continuity of the aorta with pulmonary artery banding from a left chest approach, and prefer not to add the additional repair of the often complex VSD at the initial stage.[134] Repair of the interrupted arch may be accomplished by direct aortic anastomosis, turnup or turndown of one of the arch vessels to bridge the gap, or interposition of a prosthetic graft (Fig. 80–22B). Selected patients with type B interruption have tolerated left carotid turndown to the distal aorta without cerebral insult. Alternatively, the left subclavian artery, if not small, may be brought up and anastomosed to the upper portion of the aorta. With type A interruption, the left subclavian artery arising proximal to the obstruction can be brought down in an end-to-side fashion to the descending aorta. The use of ductal tissue in any repair is considered to be unwise owing to the tendency for ductal tissue to constrict and narrow any anastomosis. Surgeons who prefer a single stage correction perform the operation with deep hypothermia, often by way of a midline sternotomy.[136–138] There is the potential for ample mobilization of the aorta to the level of the diaphragm, which allows the distal aorta to be anastomosed to the upper aorta; some surgeons claim that undue tension on the anastomosis can be avoided by use of this technique. Cardiopulmonary bypass is used for VSD closure; however, the complex location of many VSDs in association with aortic arch interruption makes early VSD closure more difficult. The combined early and late mortality from the one-stage repair has been reported to be 18 to 42%. The combined postoperative mortality after two-stage repair varies widely and is estimated to be between 35 and 72%. Further comparison of these methods should be made. Patient selection should be deliberate based on full knowledge of the variables in individual anatomy.[137]

FOLLOWUP AND OUTCOME

Infants born with interrupted aortic arch are now surviving into midchildhood, providing some perspective on followup. In all cases, it seems to be the associated malformations that dominate the clinical course. A longer period of followup may allow further evaluation of the repair of the interrupted arch itself. Reoperation for debanding and VSD repair in itself carries an additive mortality with the additional risk of complete AV block due to the extensive

Fig. 80–25. A mycotic aneurysm has developed after staphylococcal sepsis in a 6-week-old infant who had previously undergone repair of interrupted aortic arch, type B. At repair, the left carotid artery was turned down to the descending aorta and a pericardial patch was used to enlarge the anastomotic site.

approach required to close the VSD. Repairs using turndown of the carotid artery for reconstruction appear to be tolerated well on shortterm observation, with cerebral flow through the circle of Willis preserved; however, more prolonged evaluation is necessary. In most cases emergency repair of interrupted aortic arch in infancy is palliative owing to the small structures involved especially when interposition grafts are required. By early childhood gradients of at least moderate degree are measurable across reconstruction sites, and limited application of catheterization dilation procedures has been offered in this age group. For instance, it may be advantageous to relieve the moderate restenosis at the time of a catheterization prior to cardiopulmonary bypass, VSD closure, and pulmonary artery debanding with the hope of avoiding a second incision at the time of intracardiac repair that would allow inspection of the previously operated interrupted arch. It should be expected that revision of the interrupted arch will then be necessary in late childhood or after puberty if balloon dilation procedures do not provide sustained relief of residual obstruction. Anecdotal comments from a number of pediatric cardiovascular surgical centers suggest that interrupted aortic arch repair is a common cause of infants requiring prolonged (over 6 months) hospitalization after surgery, but this has not been investigated formally.

Subacute bacterial endocarditis prophylaxis is recommended indefinitely for these children. The unfortunate occurrence in an infant of a mycotic aneurysm soon after repair of interrupted aortic arch with carotid turndown has been observed (Fig. 80–25).

Prompt recognition, early successful medical management, and appropriately applied surgical techniques still do not guarantee an uncomplicated future, of course, since restoration of integrity of the aorta is often only the first step in the treatment of a patient with other complex problems. In general, however, infants born with interrupted aortic arch now have a more optimistic outcome.

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CHAPTER 81

Pulmonary Stenosis

John P Cheatham

Obstruction of blood flow from the right ventricle to the pulmonary arteries may occur at various anatomic levels. The level of obstruction may be within the right ventricle (intracavitary), at the valve, or above the valve along the pulmonary arterial tree. In the broad sense, ''pulmonary stenosis'' occurs in approximately 20 to 30% of all individuals with congenital heart disease.

In about half of these cases, the ventricular septum is intact. The basic physiologic abnormality of pulmonary stenosis with intact ventricular septum is obstruction of right ventricular output proportional to the degree of narrowing. Although the site and degree of obstruction are important, it is the presence of an intact septum that separates these individuals from patients with associated ventricular septal defect. In this chapter, we will discuss only obstructive lesions with intact ventricular septum, leaving pulmonary stenosis with ventricular septal defect and pulmonary atresia with or without ventricular septal defect to be discussed elsewhere in the book. Furthermore, we acknowledge the confusion among various ill-defined descriptive terms such as ''pure pulmonary stenosis,'' ''isolated pulmonary stenosis,'' and ''uncomplicated pulmonary stenosis.'' We have chosen the anatomic and physiologic term of ''pulmonary stenosis with intact septum'' to be understood and preferred over the anatomic term of ''pulmonary stenosis with normal aortic root'' as described by Abrahams and Wood[1] and later endorsed by Rowe.[2]

In this chapter, the following congenital cardiac defects are discussed: 1) pulmonary valve stenosis, 2) intracavitary obstruction of the right ventricle, and 3) pulmonary artery stenosis, all with intact ventricular septum.

PULMONARY VALVE STENOSIS

Background

Pulmonary valve stenosis comprises approximately 80 to 90% of all those lesions causing obstruction to right ventricular outflow. Initially described by Morgagni in 1761,[3] the pathology of the lesion was subsequently discussed by Meckel.[4] However, it was Fallot[5] who separated seven cyanotic examples of the disorder from 39 cases of the tetralogy and described a morbid term of ''trilogy'' that remains in use today, particularly by the French, to describe pulmonary stenosis, atrial septal defect, and right ventricular hypertrophy. The anatomy of pulmonary valve stenosis was nicely summarized in a monograph by Brock, who defined eight varieties of pulmonary stenosis.[6] Initially, pulmonary valve stenosis was thought to be relatively uncommon. In the first edition of her classic 1947 monograph, Dr. Taussig stated that she had not had the opportunity to study a proven case herself.[7] However, since the introduction first of cardiac catheterization and subsequently of two-dimensional and Doppler echocardiography, we now recognize that pulmonary valve stenosis is a common congenital cardiac defect.[8–13]

Prevalence

A conservative estimate of the prevalence of pulmonary valve stenosis with intact ventricular septum is that it is present in 7 to 12% of children born with congenital heart disease. Abrahams and Wood found an incidence of 11.6% of 689 cases,[1] and Campbell found 10% incidence in 1130 cases of congenital cardiac defects.[14] Rowe reported 9.9% of 15,104 cases at The Hospital

for Sick Children, Toronto, to have pulmonary stenosis.[2] Nadas and Fyler stated that although an incidence of 7.5% was found at Boston Childrens Hospital Medical Center, pulmonary stenosis may be found in up to 10 to 15% of those patients with congenital heart disease who live beyond infancy.[11]

Rose and colleagues reported different seasonal peaks of birth rate in patients with pulmonary stenosis dependent on the gender, males peaking in the fall and females in the spring.[15] Campbell found that 2.2% of siblings of patients with pulmonary stenosis also have a cardiac defect, usually pulmonary stenosis.[16] Nora and colleagues reported the probability of recurrence in siblings of pulmonary stenosis patients to be 2.9%.[17] Familial pulmonary stenosis has also been discussed by Klinge and Laursen.[10]

A recent report by Ackerman and colleagues in patients with hemophilia A supports the hypothesis that pulmonary valve stenosis can be inherited as an X-linked dominant trait.[18] Other reports suggest that dysplastic pulmonary valve stenosis in beagle dogs is not inherited as a simple mendelian trait, but rather from genes at more than one locus.[19] Mallette and associates suggested that there is a positive correlation between transient congenital hypoparathyroidism and pulmonary valve stenosis in neonates.[20]

There have been several studies regarding the incidence of congenital heart disease in offspring of parents with a specific defect and the rate among twins. Nora and Nora reported the incidence of pulmonary valve stenosis in 111 offspring with one parent having pulmonary stenosis to be 3.6%.[21] Obviously, if the mother has a mendelian syndrome such as Noonan's syndrome, half of her children will have this autosomal dominant disease. Since the incidence of congenital heart disease (mostly dysplastic pulmonary valve stenosis) is 50% in these patients, the risk for the offspring would be 25% rather than 3.6%. Finally, Anderson's report of congenital heart malformations in 109 sets of twins and triplets suggests a concordance rate up to 8.3% for monozygotic pairs and 2.2% for dizygotic twin pairs.[22]

Embryology

During cardiac septation, two endocardial cushions within the truncus arteriosus, the intercalated valve cushions, will eventually develop into the anterior cusp of the pulmonary valve and the posterior or noncoronary cusp of the aortic valve.[23] The two posterior cusps of the pulmonary valve and the two anterior or coronary cusps of the aortic valve are derived from the major truncus cushions after they have fused to form the truncus septum.[24]

The exact pathogenetic mechanism responsible for pulmonary valve stenosis is still somewhat difficult to explain. Keith suggested that there was maldevelopment of the distal portion of the bulbus cordis, from which the valves develop.[25] More and coworkers pointed out the difficulty with this theory, since the ventricular septum has already been completely formed, yet somehow a maldevelopment of the bulbus cordis leads to fusion of well-formed pulmonary valve cusps.[26] Brock suggested that there may be an abnormality of the distal bulbus cordis leading to pulmonary stenosis with sparing of the proximal bulbus, which participates in closure of the ventricular septum.[27]

Oka and Angrist have postulated that pulmonary valve stenosis may be a result of fetal endocarditis rather than a pure embryologic maldevelopment.[28] Genetic factors may play an important role. Certainly, the association of pulmonary valve stenosis and supravalve and branch pulmonary artery stenosis with multiple somatic abnormalities has been well documented.[10,17,19,21,29,30]

Anatomy and Pathology

Brock initially described eight varieties of pulmonary stenosis based on anatomic descriptions: 1) stenosis of the pulmonary valve with a normal aortic root, 2) infundibular stenosis with a normal aortic root, 3) pulmonary atresia, 4) tricuspid atresia, 5) tetralogy of Fallot, 6) double-outlet right ventricle with ventricular septal defect and pulmonary stenosis, 7) transposition of the great arteries with pulmonary stenosis, and 8) common ventricle with pulmonary stenosis.[6] Since this classic description, there have been very few studies on the pathologic anatomy of pulmonary valve stenosis. Edwards described the anatomy of the domed-shaped valve.[31] Koretzky and colleagues[32] and later Jeffrey and colleagues[33] described a type of stenosis produced by dysplastic hypertrophy of the pulmonary valve leaflets.

A more recent report by Gikonyo and co-workers beautifully described the gross and microscopic features of the anatomic pathology of 31 autopsy cases of congenital pulmonary valve stenosis.[34] They divided these specimens into six anatomic subgroups:

1) domed: 42%
2) tricuspid: 6%
3) bicuspid: 10%
4) unicommissural: 16%
5) hypoplastic annulus: 6%
6) dysplastic: 19%

In domed pulmonary valve stenosis, the valve resembles a wind sock when viewed from the pulmonary trunk (Fig. 81–1a, b). No separation into leaflets can be identified, and the base of the truncated cone is attached to the arterial trunk. Raphae are usually identified but may be either shallow or tall and variable in number. The size of the orifice varies from a pinhole to several millimeters in diameter. Microscopically, the thickening is due to an increased valve spongiosa, and the normal annulus components are deficient or absent.[34]

The unicommissural pulmonary valve is composed of a large, single leaflet and, as its name implies, has a single commissure (Fig. 81–2). The microscopic sections reveal valve thickening caused by increased fibrosa and spongiosa with the fibrous annulus replaced by myxomatous tissue.[34]

The specimens with bicuspid pulmonary valve have two leaflets and two commissures identified (Fig. 81–3). A slit-like opening of the valve is seen secondary to fused commissures. Microscopically, the leaflets are thickened as a result of increased collagen and elastic tissue, usually arising directly from the wall of the pulmonary trunk. Both the spongiosa and the supravalve annulus are absent.[34]

In tricuspid pulmonary valve stenosis, there is moderate thickening of all three leaflets and fusion of all three commissures. The microscopic section demonstrates thickened leaflets with increases in both collagen and myxomatous tissue and sparse elastic tissue.[34]

The obstruction found in "hypoplastic pulmonary valve and annulus" is due to a combination of narrowed annulus and hypoplastic, rigid leaflets. In contrast to cases with dysplastic valves, both the right ventricular infundibulum below and the pulmonary trunk above are normal. There are three diminutive, rigid leaflets with mild fusion of commissures and a markedly narrowed an-

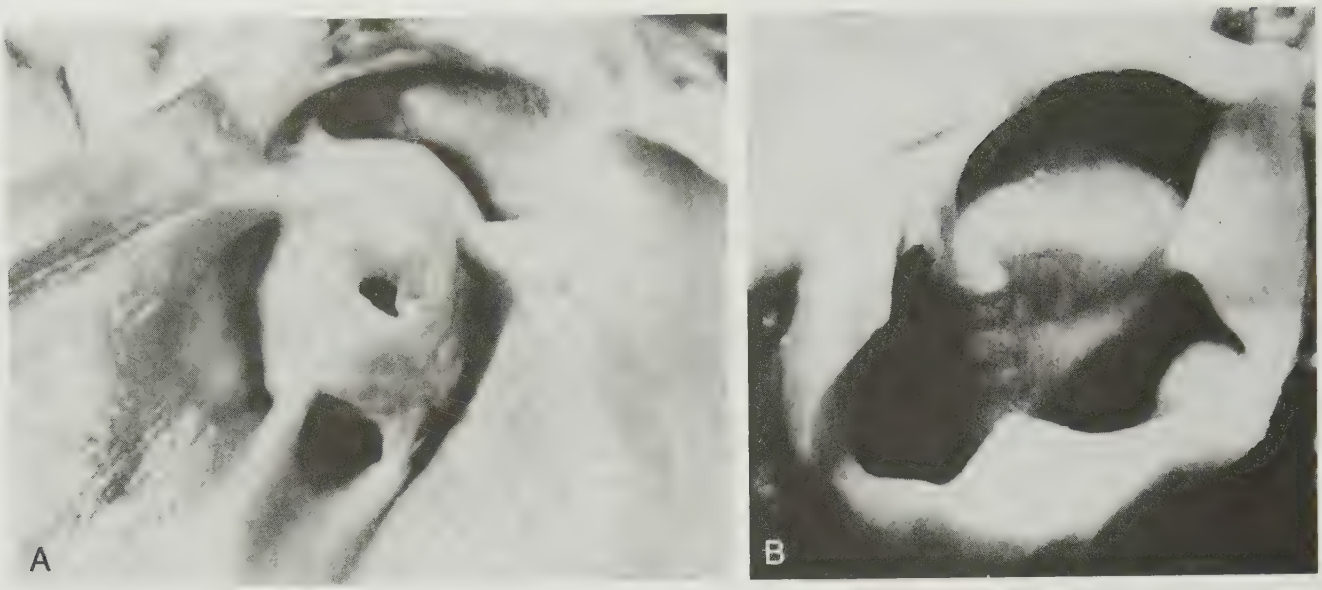

Fig. 81–1. Domed stenotic pulmonary valves in two patients. (A). Pulmonary valve viewed from above in a 21-year-old woman. Four shallow raphae are present. There is no evidence that these raphae represent fused commissures, nor is there other evidence of fusion of valve leaflets. (B). Domed stenotic pulmonary valve in a 16-day-old boy. There is a 1-mm orifice at the apex of the domed valve. Three tall raphae are present. There is no evidence that these represent fused commissures. No identifiable pulmonary valve leaflets are present. (Reproduced with permission from Gikonyo, B.M., Lucas, R.V., and Edwards, J.E.: Anatomic features of congenital pulmonary valvar stenosis. Pediatr. Cardiol., *8*:109, 1987.)

Fig. 81–2. Pulmonary valve viewed from above in a 1-day-old girl with a stenotic unicommissural pulmonary valve. The black probe is in the valve orifice and lies on top of a single commissure. A shallow raphe is present at 12 o'clock. The single valve leaflet is thickened and has a myxomatous appearance. (Reproduced with permission from Gikonyo, B.M., Lucas, R.V., and Edwards, J.E.: Anatomic features of congenital pulmonary valvar stenosis. Pediatr. Cardiol., *8*:109, 1987.)

nulus. Microscopically, the fibrosa and spongiosa components are preserved, while the supravalve annulus is elongated.[34]

Much has been written about dysplastic pulmonary valve stenosis. The gross composition of the valve consists of three markedly thickened, redundant leaflets with unfused commissures (Fig. 81–4). The obstruction to right ventricular outflow is mostly from the mass or bulk of the leaflets as well as a narrowed annulus. There is also narrowing of the right ventricular infundibulum below and the pulmonary trunk above the valve. The microscopic appearance of myxomatous valve tissue with sparse elastic fibers and poorly formed annulus are observed. Dysplastic pulmonary valves may also be present in some apparently nonfamilial cases of pulmonary stenosis and in the majority of patients with Noonan's syndrome.[2,29] Some of the anatomic and pathologic features of dysplastic pulmonary valves and hypoplastic pulmonary annuli may explain recent reports of unsuccessful balloon valvuloplasty and surgical valvotomy, which will be discussed later in this chapter.

The pathologic findings in the remaining portion of the right-sided cardiac structures are caused by secondary changes from the valve obstruction.[35] The right ventricle hypertrophies in response to the increase in afterload and is usually proportional to the degree of obstruction. The infundibular area of hypertrophy is particularly prominent; this often results in significant subvalvular obstruction. The infundibular endocardium may be opaque, with thickening of the tricuspid valve and chordal attachments. The tricuspid valve abnormalities may be the result of the mechanical stress leading to regurgitation of the valve. The right atrium may be dilated from tricuspid regurgitation or thickened from the increased pressure necessary to fill a noncompliant right ventricle. An atrial communication, either patent foramen ovale or atrial septal defect, is commonly found.

In severe pulmonary valve stenosis, small areas of myocardial

Fig. 81–3. Bicuspid stenotic pulmonary valve in a 41-year-old man who had a pulmonary valvotomy performed six years previously. The valve is viewed from above. The site of transection of the valve, outflow tract and pulmonary artery done at autopsy is noted at 2 o'clock. At the time of operation, the fused commissures were cleanly incised into the wall of the pulmonary artery. In the six years following the operation, the pulmonary valve leaflets separated considerably at the site of their original surgical incision. The two valve leaflets are thickened. The patient had no evidence of residual pulmonary valvar stenosis during life and died of hypertensive cardiovascular disease. (Reproduced with permission from Gikonyo, B.M., Lucas, R.V., and Edwards, J.E.: Anatomic features of congenital pulmonary valvar stenosis. Pediatr. Cardiol., *8*:109, 1987.)

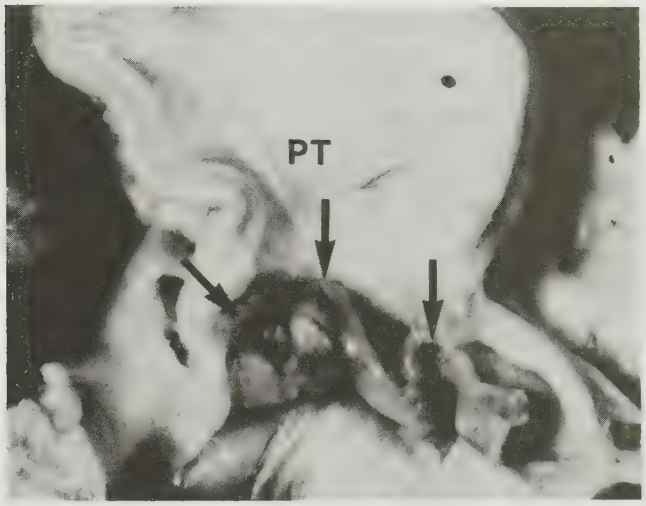

Fig. 81–4. Dysplastic pulmonary valvar stenosis in a four-month-old girl. The pulmonary trunk, pulmonary valve, and right ventricular infundibulum have been opened. The valve leaflets are thickened and completely filled the right ventricular outlet before it was opened. The arrows depict the commissures that are not fused. Note also that the pulmonary trunk is significantly narrowed just above the pulmonary valve. PT = pulmonary trunk. (Reproduced with permission from Gikonyo, B.M., Lucas, R.V., and Edwards, J.E.: Anatomic features of congenital pulmonary valvar stenosis. Pediatr. Cardiol., *8*:109, 1987.)

infarction involving the subendocardium of the right ventricular free wall and papillary muscles have been reported at autopsy.[36] This histopathologic abnormality may be more frequently found than is clinically suspected, particularly in critically ill infants with pulmonary stenosis. In sick infants with an associated large atrial shunt, the left ventricle may show significant hypertrophy.[37] However, many patients with pulmonary valve stenosis have a left ventricular dimension that is normal or increased in size. When a right aortic arch is present with pulmonary stenosis, one should be highly suspicious of a variant of tetralogy of Fallot.[38]

In the majority of patients with pulmonary valve stenosis, the main pulmonary arterial trunk is dilated with evidence of a "jet" lesion. The exception to this is in children with dysplastic pulmonary valve stenosis, in which there is usually no poststenotic dilatation. The proximal left pulmonary artery may occasionally be involved with this process. Two different mechanisms are proposed to explain this poststenotic dilatation: one involving the physics of flow dynamics, the other suggesting an intrinsic histopathologic abnormality. The more accepted mechanism states that the dilation is related to the high velocity of right ventricular output ejected through a narrowed aperture.[39,40] Using the laws of physics, the kinetic energy resulting from this high velocity must be converted to distending lateral pressure. During this process, "eddy currents" of high and low pressure occur, causing structural fatigue and stress of the elastic wall of the pulmonary artery.[41] This process may require a long period of time for dilation to occur and may explain why some newborns with significant pulmonary valve stenosis do not have poststenotic dilatation of the pulmonary trunk at birth yet develop a dilated main pulmonary artery several months later.

It is important to remember that the degree of poststenotic pulmonary trunk dilatation is frequently not proportional to the degree of pulmonary valve obstruction. In other words, patients with only mild pulmonary valve stenosis may have extremely dilated pulmonary trunks and vice versa. Therefore a second mechanism has been postulated: the poststenotic dilatation may be the result of a distinct and intrinsic abnormality of the pulmonary arterial wall. However, as in those patients with absent pulmonary valve syndrome, no definite abnormality of the pulmonary trunk has been consistently demonstrated.

Pathophysiology

The principal physiologic consequence of pulmonary stenosis with intact ventricular septum is an elevation of right ventricular pressure as a result of obstruction to right ventricular cardiac output. This rise in pressure leads to right ventricular hypertrophy that is proportional to the degree of obstruction. As a practical

matter, it is helpful to separate pulmonary valve stenosis physiology into two types: severe and mild-to-moderate.

The work of Rudolph allowed us to improve our understanding of the fetal physiologic abnormalities of pulmonary stenosis.[42] As the obstruction develops, an increase in right ventricular muscle mass occurs (from both hyperplasia and hypertrophy of the muscle fibers) that is proportional to the severity of stenosis. The fetal or neonatal response to an increase in afterload is apparently different from that of the adult myocardium. The mature animal myocardium usually hypertrophies in response to obstruction with very little hyperplasia noted. Since hypertrophy of the myocardial cell is not associated with an increased number of capillaries and hyperplasia is associated with capillary growth, one can speculate how the fetal or neonatal myocardium has several advantages over the adult myocardium. In the immature animal, the relationship between the myocardial cell and capillaries remains constant; this may allow the individual the ability to generate high ventricular pressure that maintains normal cardiac output across severe obstruction.[42]

There are a few hemodynamic characteristics worthy of discussion that clearly distinguish pulmonary valve stenosis with intact ventricular septum from other types of right ventricular outflow tract obstruction, such as tetralogy of Fallot. In the patient with an intact septum, the pressure generated in the right ventricle may be higher than that in the left ventricle. In addition, for a comparable degree of pulmonary stenosis, patients with an intact septum may be able to establish better pulmonary flow with better exercise tolerance than do children with tetralogy of Fallot.[11] The limiting factor to increasing cardiac output appears to be the noncompliant right ventricle, which is unable to fill, thus limiting output.

The pressure rise during right ventricular contraction occurs progressively to an early systolic peak followed by a fall in pressure. Since emptying of the right ventricle depends upon the amount of resistance at the orifice in patients with pulmonary valve stenosis, the peak of contraction occurs later in systole as the severity of obstruction increases. Normal cardiac output is maintained at the expense of right ventricular hypertrophy. Clinically, right-sided heart failure with right ventricular dilatation is seen in two separate groups of patients. It may occur in newborns with critical pulmonary valve stenosis who are unable to cope with the cardiac demands of the body. Right heart failure is also seen in rare individuals who are not recognized to have severe pulmonary valve stenosis with right ventricular hypertrophy. Eventually, usually in early adulthood, right ventricular dilatation may occur with subsequent congestive failure. Pulmonary flow decreases with right ventricular failure, but systemic oxygenation may be normal at rest. With an increase in cardiac demand, such as with exercise, symptoms of right-sided congestive heart failure occur. Cyanosis is a relatively late occurrence in these patients and may be the consequence of one or two mechanisms. It may be secondary to greatly diminished cardiac output and an increased oxygen extraction at the capillary level or the result of a right-to-left shunt at the atrial level. The atrial right-to-left shunt depends upon the increase in right atrial pressure as a result of decrease in right ventricular compliance with an increase in end-diastolic ventricular pressure. It is noteworthy that in experimental animal studies, right-sided failure occurred only when the diameter of the pulmonary artery was reduced to less than one third of its original size.[43]

Williams and colleagues described a syndrome of underdeveloped right ventricle with pulmonary stenosis that may present as cyanosis in the neonate.[44] Because of the hypoplastic right ventricle, the compliance of the ventricle is decreased with subsequent right-to-left atrial shunting.[10,44–47] Right ventricular compliance may be decreased by endocardial fibrosis as a result of subendocardial ischemia documented in a few infants with severe pulmonary valve stenosis.[36] With the altered right ventricular compliance found in severe pulmonary stenosis, a tall, peaked A wave is often seen in the right atrium. It is also important to remember that in many patients with severe pulmonary valve stenosis and intact ventricular septum, tricuspid insufficiency occurs. This physiologic event may alter right atrial pressure, with a large V wave and an increase in mean pressure, with subsequent effects on cardiac output and symptoms depending on the presence or absence of an interatrial communication.

Manifestations

Clinical Features

Clinically, pulmonary valve stenosis with intact ventricular septum is best described as either mild-to-moderate or severe. Rowe reported equal frequency of both grades.[2]

Mild-to-Moderate Stenosis. Patients with mild pulmonary valve stenosis are asymptomatic, while some individuals with moderate stenosis may later develop mild dyspnea and fatigue with exertion. Growth and development in these children are usually normal unless a significant associated cardiac defect is present. Cyanosis is absent in individuals with mild pulmonary stenosis and rare in those with moderate obstruction. It is worthwhile to note that cyanosis is not a reliable criterion for assessment of severity in pulmonary stenosis.

The jugular venous pulse is usually normal, and there are no signs of congestive heart failure. The precordium is quiet, with a palpable systolic thrill rarely present. A few patients demonstrate a tapping right ventricular–type impulse. The physical appearance of the children is usually normal, although 20% of the patients in the Toronto series demonstrated the moon facies and chubby features previously described by Wood.[2,48]

The striking auscultatory feature of pulmonary valve stenosis is a prominent systolic, ejection-type murmur. The murmur may vary in length and intensity, but it usually ends before the aortic valve closure. The maximum intensity of the murmur is at the upper left sternal border radiating to the back; the murmur is also heard along the precordium and neck. The phonocardiogram demonstrates a crescendo–decrescendo characteristic with a peak in mid- to late systole depending on the severity (a later peak with more severe stenosis) and with a medium or high frequency.[49–51] The duration of the murmur in mild stenosis is shorter with a peak that seldom passes midsystole. In contrast, patients with tetralogy of Fallot with severe stenosis also have a short systolic ejection murmur that peaks early in systole. The murmur of pulmonary valve stenosis increases in duration and intensity after inhalation of amyl nitrate (or other vasodilating agents), whereas the opposite is true in children with tetralogy of Fallot.[52] It is also important to remember that patients with combined moderate infundibular and valvar pulmonary stenosis may also have a systolic ejection

murmur along the fourth intercostal space as well as in the usual higher location. A soft, early, decrescendo diastolic murmur may infrequently be heard in the second left interspace and represent mild pulmonary regurgitation. More likely, a low-frequency mid-diastolic murmur over the tricuspid or mitral valve may be heard; this should heighten suspicion of an associated large atrial or ventricular septal defect, respectively.

A high-pitched ejection sound or systolic click is usually heard in mild-to-moderate pulmonary valve stenosis. It is frequently heard along the second or third left intercostal space, but it may also be audible along the lower sternal border.[53] This sound usually occurs early in systole, 0.08 s after the Q wave, and may be confused with wide splitting of the first heart sound.[54,55] It can usually be distinguished by its sharp, high-pitched quality, by the location, and by the click becoming louder during expiration. The click sound most likely originates from the sudden opening and doming of the thickened but compliant stenotic valve found in mild-to-moderate stenosis.[53] An alternative mechanism of etiology, but one that is less accepted, is the sudden expansion of the pulmonary arterial wall.[53,56] An inverse relationship between severity and the Q–click interval on the phonocardiogram has been found:[57] as the severity increases, the systolic ejection click occurs earlier, to the point at which it may be indistinguishable from the first heart sound. Important correlations of respiratory changes in the click to severity have been made.[53] Hultgren found that when the diastolic pressure of the pulmonary arteries consistently exceeded the right ventricular end-diastolic pressure, a click was present in all phases of the respiratory cycle. In contrast, if the right ventricular end-diastolic pressure exceeded the pulmonary artery diastolic pressure during inspiration, no click was recorded. Later, Weyman and colleagues' echocardiographic work supported these observations.[58]

The second heart sound in children with mild-to-moderate pulmonary valve stenosis is usually split and of normal intensity. The degree of splitting is directly proportional to the severity of obstruction. This correlation between degree of stenosis and width of splitting of the second heart sound was demonstrated by phonocardiograms and simultaneous right ventricular pressure measurements.[50,55] Thus in patients with mild-to-moderate stenosis, the second sound varies normally with respiration. A fixed, widely split second heart sound with mild pulmonary valve stenosis should alert one to the possibility of an associated atrial septal defect.

There also appears to be an inverse relationship between the severity of stenosis and the intensity of the pulmonary component of the second sound.[50,55] As the severity of the pulmonary valve stenosis increases, the intensity of the closure sound of the pulmonary valve decreases. Occasionally, in mild stenosis with markedly dilated main pulmonary artery, the pulmonary closure sound may actually be louder than normal.[59,60] The first heart sound is unremarkable, and the blood pressure and peripheral pulses are usually normal in children with mild-to-moderate pulmonary valve stenosis.

Severe Stenosis. Conventionally, severe pulmonary valve stenosis usually implies a resting right ventricular pressure equal to or greater than left ventricular pressure or a transvalvular gradient exceeding 80 mm Hg. Most patients in this group have signs or symptoms, although up to 25% are asymptomatic.[2] Central cyanosis is one of the most important signs in patients with severe stenosis and some form of atrial communication.[61,62] However, mild peripheral cyanosis may be present in severe obstruction with intact atrial septum and low cardiac output.[14,63] The central cyanosis depends to a large extent on the amount of right-to-left atrial shunting. Most patients with an atrial communication can be demonstrated to have some degree of right-to-left shunting at rest or with exercise by indicator dye dilution curves, contrast echocardiography, or pulse-oximetry. In the Toronto series, two thirds of children with severe pulmonary stenosis had right-to-left atrial shunting.[2] However, only 15% were moderately or markedly cyanosed, and 20% had clubbing of the fingers. At least during the childhood years, clinically apparent and significant central cyanosis and clubbing is unusual, although a small degree of central right-to-left shunting is common in these patients.

It has been postulated that the degree of central cyanosis may be progressive with age if the relative size of the shunt increases. Campbell found that 10% of 44 cyanotic patients with severe pulmonary valve stenosis and intact ventricular septum were cyanotic at birth, while 25% were cyanotic by four years of age, the remainder becoming cyanotic later in life.[14] In this group, the average age of onset of cyanosis was 14.4 years. In the Toronto series, 25% were cyanotic at birth, 50% by one year of age, and 67% by five years.[2] Although squatting has been reported, most of these cases have subsequently been diagnosed to have tetralogy of Fallot. Therefore squatting as a principal symptom of severe pulmonary valve stenosis with intact ventricular septum should be scrutinized, and other forms of congenital heart disease should be considered.

Children with severe pulmonary stenosis may have dyspnea and fatigue even with a moderate degree of exercise. All of the cyanotic patients in the Toronto series exhibited exertional dyspnea.[2] In older patients, episodes of chest pain and syncope have occurred with exercise.[1,14,64] Marquis reported an instance of sudden death in a patient with severe pulmonary valve stenosis.[65] In another report, a 3½-year-old child complained of epigastric pain after exercise and subsequently died from right ventricular free wall and septal infarction.[66] Many of the symptoms in this group of patients are related to critically low cardiac output during exercise and inadequate myocardial blood flow. It is possible that this pathophysiologic process may lead to cardiac arrhythmias.[2]

Growth and development in infants with severe pulmonary stenosis are usually normal, without evidence of wasting. In the Toronto series, 50% of patients with severe pulmonary stenosis have the moon facies and chubby phenotype.[2,48] It is wise to remember that moon facies is a common finding in healthy-appearing, normal children and is not a pathognomonic feature of pulmonary valve stenosis.

Prominent A waves in the jugular venous pulse are frequently seen in patients with severe pulmonary valve stenosis. These pulsations may be palpated in the liver as well but are not a consistent finding. In cases with right-sided failure secondary to severe pulmonary stenosis, a prominent V wave in the jugular venous pulse may overshadow the A wave and represent significant tricuspid valve insufficiency.

Precordial palpation may demonstrate evidence of cardiomegaly in patients with severe pulmonary valve stenosis and cardiac decompensation. The apical beat is tapping in quality with a right ventricular heave. Abrahams and Wood placed a great deal of importance on this sign, since it is lacking in moderate cases of

pulmonary stenosis or in patients with tetralogy of Fallot.[1] Later, Schmidt and Craige quantitated this observation in children.[67]

A systolic thrill is almost always palpated in the pulmonic area but may also be felt in the suprasternal notch, in the left carotid artery, and even along the lower sternal border. The systolic thrill may be absent in very young infants with severe pulmonary valve stenosis and in those with congestive heart failure and low cardiac output. Radiation of the thrill into the neck has led to a mistaken clinical diagnosis of aortic stenosis on occasion.

The systolic murmur of severe pulmonary valve stenosis is maximal at the second and third left interspaces, radiating to the back, neck, and rest of the precordium. The murmur is usually loud, harsh, and long in quality. In severe stenosis, the peak occurs later in systole. It is generally true that the murmur of severe stenosis is loud. Dimond and Lin found no relationship between the murmur's intensity and peak right ventricular pressure.[66] Mannheimer and Jonsson later disputed this finding,[68] and the Toronto series reported that no infants dying with severe pulmonary valve stenosis had less than a grade 3 systolic murmur.[2] In young infants with severe stenosis and congestive heart failure, the systolic murmur of tricuspid insufficiency may predominate, with very little murmur noted over the pulmonary area.

When the systolic ejection click occurs earlier, it signifies more severe stenosis. Many times, this ejection sound cannot be separated from the first heart sound. The first sound is usually normal. In severe stenosis, it is difficult to assess the respiratory splitting of the second heart sound. When the obstruction is critical, the second sound is not audible at the left upper sternal border, the aortic component being obscured by the long systolic murmur and the pulmonic sound being too soft to be clinically apparent. Various investigators have found a combination of the Q–ejection click interval, Q–peak magnitude of the murmur, and semilunar valve closure interval to be very useful in estimating the severity of right ventricular hypertension by noninvasive means.[55,57] This is currently of limited practical applicability because of the use of continuous-wave Doppler estimation of severity of pulmonary valve stenosis, which is discussed later in the chapter.

It is sometimes difficult to make clinical estimates of the severity of pulmonary valve stenosis in patients with Noonan's syndrome or, more specifically, in individuals with dysplastic pulmonary valves. The redundancy of the tissue usually abolishes the systolic ejection click and also alters splitting of the second sound. Therefore one has to be very careful about assessing severity of stenosis in these individuals.

Electrocardiogram

The electrocardiogram has been used extensively in the assessment of severity in patients with pulmonary valve stenosis.[2,11,35,57,69–72] In mild stenosis, the electrocardiogram may be normal in 30 to 65% of individuals.[1,66,73,74] Frequently, the only abnormality is a slight rightward deviation of the mean QRS frontal plane axis. The R wave in the right precordial leads usually is less than 10 to 15 mm. Both Ellison and Restiaeux[70] and Fowler and colleagues[71] have shown that QRS conduction delay is characteristic of mild pulmonary stenosis. These authors also showed that only 4% of patients with mild stenosis have complete right bundle branch pattern. The P and T waves are usually normal.

A normal electrocardiogram in moderate pulmonary valve stenosis is the exception, being present in only 10% of cases.[35] There tends to be some right axis deviation and inversion of the R/S ratio in V_1. The R wave is usually less than 20 mm with an R/S ratio greater than 4/1 (Fig. 81–5). The P waves are usually normal. Approximately 50% of patients have upright T waves in the right precordial leads.

The electrocardiogram is almost always abnormal in patients with severe pulmonary stenosis, with very few exceptions. There may be extreme right axis deviation, frequently greater than 150°. In the right precordial leads, a qR, Rs, or a pure R wave is usually present, the magnitude of the R wave being greater than 20 mm (Fig. 81–6). The R/S ratio in V_1 is reversed, while the R/S ratio in V_6 may be less than 1.0 in severe stenosis. The P waves are abnormally tall and peaked in lead II and the right precordial leads, indicative of right atrial enlargement. The T waves may be upright or inverted in the right precordial leads with occasional ST changes suggestive of ischemia.[57]

Before Doppler echocardiography was routinely available, the

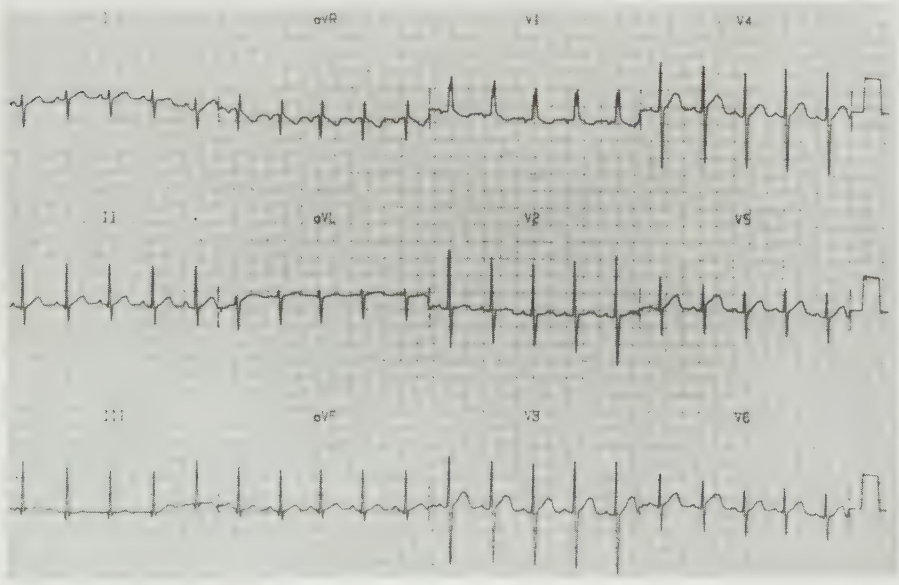

Fig. 81–5. An electrocardiogram in a four-year-old girl with moderate pulmonary valve stenosis. Right axis deviation (QRS axis of +120°) and right ventricular hypertrophy are frequently seen. As in this case, the R wave is usually less than 20 mm in lead V_1 with an R/S ratio greater than 4/1. The T waves are flattened in V_1 but are upright in V_2.

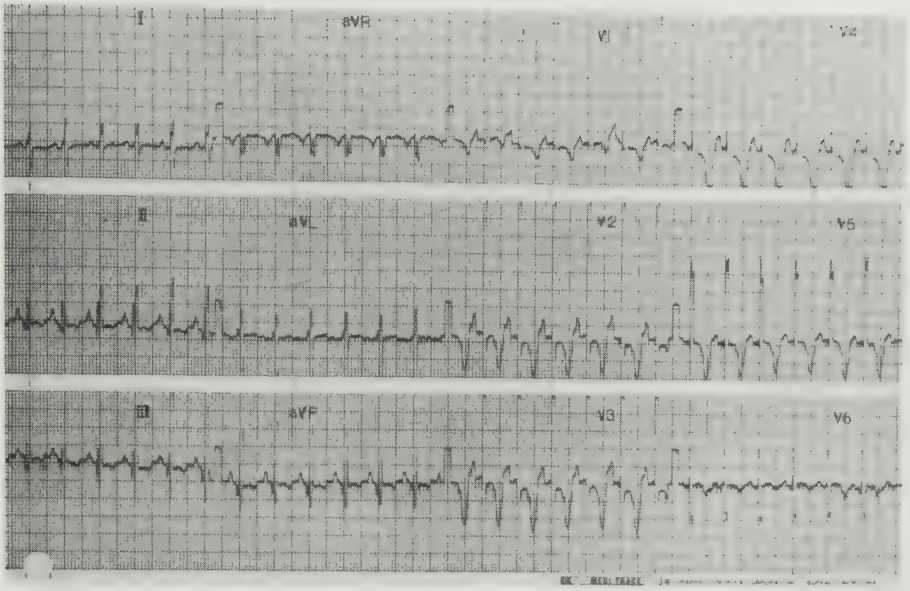

Fig. 81–6. An abnormal electrocardiogram in a three-day-old with severe pulmonary valve obstruction. A qR pattern is observed in lead V_1 with an R wave greater than 20 mm, indicating significant right ventricular hypertrophy. Although not present in this case, T waves and ST segments may suggest ischemia.

resting right ventricular pressure was estimated by using the electrocardiogram of patients between 2 and 20 years old with pulmonary valve stenosis:[42] RV pressure in millimeters of mercury equals the R wave amplitude (in millimeters) in V_4R or $V_1 \times 5$ if a pure R wave is present. Predictive equations also have been developed by using data obtained during the U.S. Joint Study of Congenital Heart Defects.[75,76] As expected, the most important variables were the auscultatory findings and the electrocardiogram. An estimation of the pressure gradient across the pulmonary valve was given by the following equation:

$$\text{Pressure gradient right ventricle to pulmonary artery (mm Hg)} = 10.5(\text{ISM}) + 2.6(S_1) + S_2 \text{ score} + \text{T score}$$

where ISM = intensity of systolic murmur graded 1 to 6; S_1 = S wave in lead I in millimeters, where 1 mm = 0.1 mV; S_2 score = -10 if P_2 is normal, $+2$ if P_2 is audible but diminished, and $+15$ if P_2 is inaudible; T score = $+15$ if T wave in V_1 is diphasic when R wave in V_1 is greater than 10 mm, otherwise the T score = 0. The above equation is seldom used today to assess the severity of pulmonary valve stenosis, but the informal judgment of severity in the clinic takes these variables into consideration in a less quantitative manner.

Occasionally, infants or newborns with severe pulmonary valve obstruction have a QRS axis that is more "leftward" than expected, between 30° and 60°, with left ventricular hypertrophy and right atrial enlargement.[77] In the older patients discussed by Williams and colleagues, more left ventricular voltage and less right ventricular hypertrophy were found in patients with underdeveloped right ventricles.[44] Ellison and Restiaeux reported the association of left axis deviation with superior frontal plane loop in some patients with pulmonary stenosis.[70] It is unclear from the report whether there is a direct relationship between this electrocardiographic abnormality and Noonan's syndrome, associated cardiomyopathy, or possibly an associated endocardial cushion defect.

Chest Roentgenogram

The roentgenographic features of pulmonary valve stenosis with intact ventricular septum have been well described by various authors.[2,12,78–84] The most consistent and distinctive radiographic feature is a prominent main pulmonary artery segment secondary to poststenotic dilatation of the pulmonary trunk and proximal left pulmonary artery (Fig. 81–7). This finding is present in up to 90% of patients with pulmonary valve stenosis, but it may be absent in infants, small children, and patients with dysplastic pulmonary valves.[9,33] The cardiac apex is usually down-pointing and rounded. Only rarely in severe obstruction without failure is uptilting noted. The right cardiac border is not suggestive of right atrial enlargement, except in severe cases with tricuspid insufficiency or moderate obstruction with atrial septal defect. However, in one series, up to 50% of patients with pulmonary stenosis were found to have prominence of the right atrial segment.[35] The aortic arch is almost always left-sided, and the left atrial shadow is normal.

In cases of mild-to-moderate pulmonary valve stenosis, the heart size and pulmonary vascular markings are usually normal. If there is severe obstruction without cardiac decompensation, there may only be mild cardiac enlargement. When right-sided cardiac failure occurs, the chest roentgenogram demonstrates cardiomegaly with a "globular-shaped" heart, prominent right atrial shadow, and diminished pulmonary vascular markings (Fig. 81–8). Pulmonary vascularity is seldom increased unless there is a significant left-to-right shunt at the atrial, ventricular, or ductus arteriosus level. Decreased pulmonary vascular markings may be found in severe cases with a right-to-left shunt.

Echocardiogram

The noninvasive evaluation of abnormalities of the pulmonary valve by M-mode and two-dimensional echocardiography was less than satisfactory in the past.[58,85] However, with the recent advances in imaging capabilities, Doppler echocardiography, and color flow mapping techniques, the sensitivity and specificity in detecting valvular abnormalities have drastically improved.[86–99]

M-mode. M-mode echocardiography can help diagnose pul-

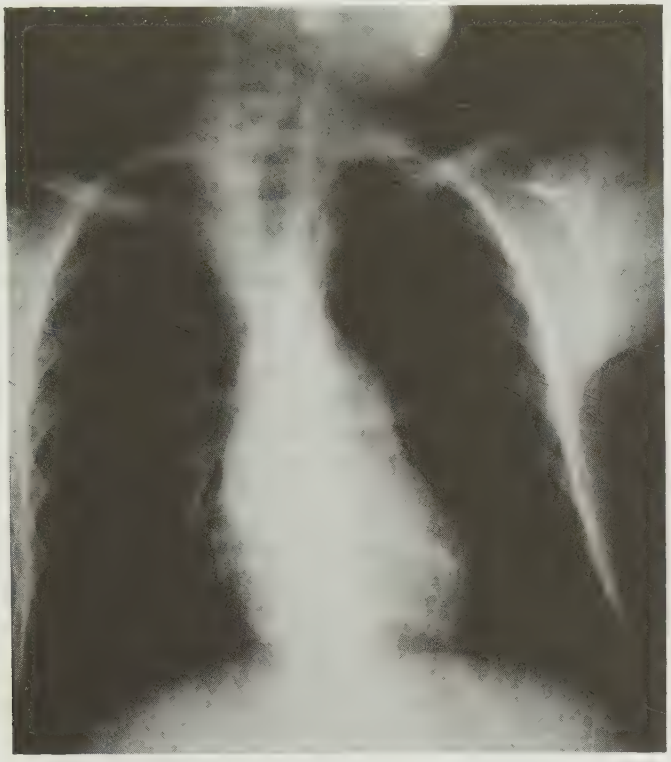

Fig. 81–7. A chest roentgenogram from an 8-year-old boy with mild stenosis of the pulmonary valve. The heart size is usually normal. The pulmonary vascular markings are unremarkable. The most distinctive radiographic feature of this disease is poststenotic dilatation of the pulmonary trunk as depicted here. The degree of dilatation is unrelated to the severity of stenosis.

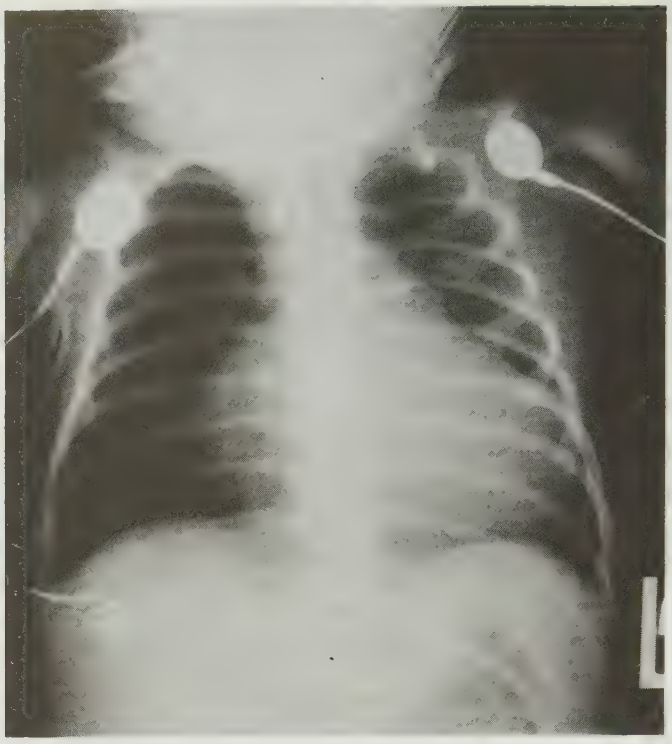

Fig. 81–8. The chest roentgenogram of a newborn with severe pulmonary valve stenosis and intact ventricular septum. There is cardiomegaly with a globular configuration of the heart. The right atrial shadow is prominent and may represent dilatation secondary to tricuspid valve insufficiency. The peripheral pulmonary vascular markings are diminished.

monary valve stenosis, but it has certain limitations.[58,85,100] The diagnosis is based upon the altered hemodynamics affecting the right ventricle and pulmonary artery pressure and their effect upon the motion of the pulmonary valve.[58] With decreased right ventricular compliance, the ventricular end-diastolic pressure exceeds the simultaneous pulmonary artery pressure with a resultant presystolic opening of the pulmonary valve.[53,101] This opening of the valve following atrial contraction corresponds to the exaggerated posterior deflection of the posterior pulmonary valve leaflet (A dip) on the M-mode echocardiogram. In addition, the motion of the pulmonary valve opening is reduced. Children with significant pulmonary valve stenosis may demonstrate right ventricular free wall and ventricular septal hypertrophy as noted on the M-mode echocardiogram.

Unfortunately, the M-mode echocardiographic diagnosis of pulmonary valve stenosis has a number of limitations:[102]

1) The pulmonary valve may be difficult to record, preventing visualization of the diastolic motion pattern.
2. The technique does not permit direct visualization of the stenotic valve, but rather provides indirect diagnostic information based on the effects of abnormal presystolic pressure gradient on pulmonary valve motion.
3. The exaggerated A dip in valve stenosis is not specific and may occur in any condition in which right ventricular end-diastolic pressure exceeds simultaneous pulmonary artery pressure, e.g., Uhl's anomaly.
4. M-mode echocardiography is not generally useful in patients with mild pulmonary valve stenosis, since the hemodynamic abnormalities are not reflected on the pulmonary valve echogram.[103]

For all of these reasons, M-mode echocardiography has very limited diagnostic capabilities in children with pulmonary valve stenosis.

Two-Dimensional Echocardiogram. Two-dimensional echocardiography has become the most widely used noninvasive imaging technique for the evaluation of children with congenital heart disease. By enlarging the area to be investigated and displaying the echocardiogram in an appropriate spatially oriented format, the two-dimensional echocardiogram allows direct visualization of the abnormal pulmonary valve leaflets and the structural consequences of the abnormal flow upon other cardiac structures. Weyman and colleagues reported several important differences in the appearance and motion pattern of the pulmonary leaflets in patients with pulmonary valve stenosis compared to normal individuals:[102]

1) During systole, the leaflets do not lie parallel to the margin of the pulmonary artery, but rather curve inward toward the midportion of the pulmonary trunk. This reflects doming of the pulmonary valve and narrowing of the orifice (Fig. 81–9).
2) The proximal portion of the leaflet echogram moves through a wide arc while the distal tips remain relatively close to-

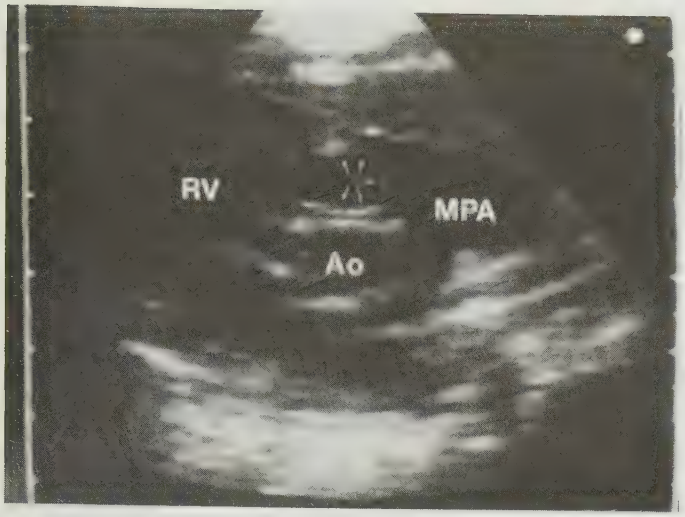

Fig. 81–9. A two-dimensional echocardiogram in an infant with moderate pulmonary valve stenosis. A parasternal right ventricular outflow tract view demonstrates systolic doming of the pulmonary valve leaflets, as outlined by the arrows. The right ventricle (RV), main pulmonary artery (MPA), and aorta (Ao) are also seen.

gether, resulting in an increasingly obtuse angle between the leaflet echoes.

3) Although the pulmonary valve echoes are indistinguishable from normals during most of diastole, the leaflets frequently move to a fully open or domed position following atrial systole in patients with pulmonary valve stenosis.

The actual visualization of the thickened pulmonary leaflets, pulmonary valve annulus, dilated pulmonary trunk, hypertrophic right ventricle, and other associated congenital heart defects are possible with two-dimensional echocardiography. Although the advantages of two-dimensional echocardiography over M-mode echocardiography are apparent, definitive diagnosis of pulmonary valve stenosis by imaging alone is difficult. In Weyman's series, only 64% of patients undergoing two-dimensional echocardiography had adequate visualization of both the anterior and posterior leaflets.[102] Gutgesell and co-workers demonstrated the difficulty in prospectively diagnosing pulmonary valve stenosis by two-dimensional echocardiography alone.[104] The sensitivity of two-dimensional echocardiography was only 76%, misdiagnosing six patients with gradients ranging from 28 to 70 mm Hg. There were also four false-positive diagnoses with a specificity of 97%. As a matter of fact, out of the six most common congenital heart defects, pulmonary valve stenosis was the most difficult to predict with accuracy by two-dimensional echocardiography. In addition to the standard left parasternal short-axis and long-axis views to evaluate the pulmonary valve, the subcostal elongated right oblique view has improved imaging of the right ventricular outflow tract, while the suprasternal notch technique has allowed greater visualization of the pulmonary arteries.[105,106]

Doppler Echocardiogram. It has become quite apparent that with the addition of pulsed and continuous-wave Doppler echocardiography, the detection and prediction of severity of pulmonary valve stenosis have significantly improved.[91,94–96,99,107–109] The Doppler sample volume is moved across the pulmonary valve until the maximal frequency shift, determined by the audible signal, is obtained. Sampling is performed with either an imaging or a nonimaging continuous wave probe from both the high left parasternal surface and subcostal plane, taking care to minimize the angle of incidence between the Doppler signal and the main axis of the pulmonary trunk. The recorded peak flow velocity on spectral display is converted to estimated pressure gradient utilizing the modified Bernoulli equation: $PG = 4V^2$, where PG = instantaneous pressure gradient in millimeters of mercury, and V = peak Doppler velocity in meters per second.[94] Published data have demonstrated that the Doppler-estimated transvalvular gradient in patients with pulmonary valve stenosis correlated well with that obtained from strain-gauge manometry during cardiac catheterization.[88,91,99]

There are important considerations to remember in using Doppler echocardiography to estimate the severity of pulmonary valve stenosis. Doppler velocities represent an instantaneous pressure relationship, whereas recordings obtained at cardiac catheterization are peak-to-peak systolic gradients and may not be directly comparable. The instantaneous gradient is normally greatest in early systole, well before the nonsynchronous peak-to-peak gradient. However, this is less of a practical problem with pulmonary stenosis than with aortic stenosis. Since aortic systolic and pulse pressures are greater in amplitude than those found in the pulmonary artery, the difference between maximal instantaneous and peak-to-peak pressure gradients is less evident in pulmonary valve stenosis than in aortic valve stenosis. For the Doppler estimate to be accurate, a jet must be formed, and this may not occur with small orifices, a factor that causes underestimation of high gradients.[110,111] It is extremely important for the patient to be in a similar hemodynamic state during the echocardiogram and at the time of cardiac catheterization if comparable estimates of severity are to be obtained. In the younger child or infant, sedation prior to the echocardiogram is frequently advised.

New Imaging Techniques. The color-coded, two-dimensional Doppler echocardiogram is able to demonstrate blood flow imaging with simultaneous morphologic imaging. By convention, flow directed away from the transducer is coded as various shades of blue, depending on the velocity, while flow toward the transducer is coded with various shades of red. Extremely turbulent and high-velocity flow patterns, as seen in valvular stenotic lesions, demonstrate a blend of colors, giving rise to green or white. Color flow mapping has nicely demonstrated the abnormal "jet" flow pattern in patients with pulmonary valve stenosis (Fig. 81–10).[112,113] Valdes-Cruz and colleagues suggested a potential error in the estimation of peak instantaneous gradients in the clinical setting using only conventional Doppler echocardiography without color flow mapping to define the spatial orientation and width of stenotic jets.[97,98] This new technique certainly demonstrates promise in improving the accuracy in the detection and prediction of severity in pulmonary valve stenosis.

Contrast echocardiography using the intravenous injection of agitated normal saline solution has also been used in the diagnosis of various congenital heart defects.[114] Its usefulness in the detection of pulmonary valve stenosis is limited, but this technique is very useful to demonstrate right-to-left atrial shunting associated with the obstructive lesion. Color flow mapping may potentially alleviate the need for contrast echocardiography.

X-ray-computed tomography (CT) has been used widely for examination of many organ systems. More recently, with gating

Fig. 81–10. A color-coded two-dimensional Doppler echocardiogram in a child with moderate stenosis of the pulmonary valve. A parasternal right ventricular outflow tract view is performed with imaging of the distal outflow tract, pulmonary valve, and main pulmonary artery. Normal, laminar flow in the right ventricular outlet proximal to the pulmonary valve is color-coded as blue, since the flow is directed away from the transducer. However, spectral dispersion occurs at the stenotic pulmonary valve with turbulent flow transmitted into a dilated pulmonary trunk. This abnormal turbulent flow is color-coded as green with shades of yellow and white. In addition, shades of orange and red are seen in the proximal and lateral pulmonary trunk, representing "aliasing."

of the electrocardiogram, cardiac CT was used to asssess the morphology of various congenital heart defects.[115] Although its use in the diagnosis of pulmonary valve stenosis has been limited, the technique may offer advantages in the quantitative assessment of pulmonary arteries.

Magnetic resonance imaging (MRI) has recently been shown to provide excellent tomographic images of congenital heart defects.[116–119] Jacobstein and associates compared electrocardiogram-gated MRI with two-dimensional echocardiography in evaluating children with congenital heart disease.[120] In general, two-dimensional echocardiography was superior in the evaluation of intracardiac defects and valvular abnormalities, but MRI provided very useful information in the evaluation of aortic arch anomalies and palliative systemic to pulmonary artery shunts. It is also possible that magnetic resonance spectroscopy may be used to evaluate the myocardial energy demands using cardiac phosphorus as a substrate.[121] This may provide a means to evaluate the metabolic cost of specific structural cardiac defects, particularly those affecting ventricular performance, such as pulmonary valve stenosis. Magnetic resonance spectroscopy and positron emission tomography, which are still in their "infancy" stage in the evaluation of children with congenital heart disease, are discussed elsewhere in this text. They may provide the pediatric cardiologist with a new powerful set of tools to be used in the evaluation of children and young adults born with pulmonary stenosis.

Cardiac Catheterization

The role of cardiac catheterization and angiography in the diagnosis and treatment of pulmonary valve stenosis has changed dramatically over the past five years. In the past, hemodynamic and angiographic information was required to select those patients requiring surgical valvotomy and to aid the surgeon in more precise anatomic and physiologic detail. However, since balloon pulmonary valvuloplasty has become the treatment of choice in patients with significant pulmonary valve stenosis, the indications for cardiac catheterization have changed. It is also true that with the use of two-dimensional and Doppler echocardiography providing the diagnosis and determining of the severity of obstruction, the indications for diagnostic cardiac catheterization have been significantly reduced. It should be emphasized that the pediatric cardiologist should use all available information, such as clinical exam, electrocardiogram, chest roentgenogram, two-dimensional or Doppler echocardiogram, and possibly color flow mapping, in an attempt to determine who should undergo catheterization.

Hemodynamics

In patients with pulmonary valve stenosis and intact ventricular septum, the oximetry data depends upon the severity of obstruction and the association of intracardiac or extracardiac shunts, that is, atrial septal defect and patent ductus arteriosus. In mild-to-moderate stenosis with small atrial communication, the oxygen saturations are usually normal. A small amount of bidirectional atrial shunting may be present undetected by oximetry but demonstrated by contrast echocardiography, color-flow Doppler mapping, or indicator dye dilution technique. When the valve stenosis is severe and there is an atrial communication, there is frequently right-to-left shunting with a resultant lower oxygen saturation in the left atrium, left ventricle, and systemic artery than the saturation found in the pulmonary vein. If there is a large atrial septal defect without severe stenosis, there will usually be evidence of left-to-right shunting as measured by oximetry. When a significant patent ductus arteriosus is present, left-to-right shunting into the pulmonary artery is found with increased oxygen saturations compared to those found in the right ventricle.

The most important hemodynamic parameters obtained during cardiac catheterization are the measurements of right ventricular pressure in comparison to systemic arterial pressure and the gradient across the site of obstruction. Carefully performed catheter withdrawal with an end-hole catheter from the pulmonary artery wedge position to the right ventricle will reveal both the site and degree of obstruction. A peak right ventricular systolic pressure less than 35 mm Hg and a systolic gradient across the valve less than 10 mm Hg are considered within normal limits.[122]

The right ventricle generates energy to pump blood through the pulmonary circulation that may be expressed as kinetic energy (velocity) or as potential energy (pressure). Several authors quantitated the relationship between the severity of obstruction and the pressure drop across the valve, but it was Gorlin and Gorlin who expressed this as a pulmonary valve area.[123] Later, several investigators observed the presence of a systolic depression of the main pulmonary artery pressure recording compared to the distal pulmonary artery systolic pressure in patients with significant pulmonary valve stenosis.[124–126] Muster and colleagues emphasize two reasons for the unusual pressure patterns found in patients with pulmonary valve stenosis: 1) increased blood velocity in the main pulmonary artery and 2) architecture of the main pulmonary artery and the right and left branches.[127] As blood accelerates through the stenotic pulmonary valve, more of the total energy is expressed as kinetic energy, a process that results in a drop in pressure, the so-called Bernoulli effect. In addition to the Bernoulli effect (con-

vective acceleration), there are two additional causes for pressure loss: 1) local acceleration secondary to the change in blood velocity over time and 2) frictional losses. However, several studies indicate that it is the Bernoulli effect that predominates in the fall of pressure.[128–130] A negative systolic pressure, owing to a Venturi effect, may also be recorded in patients with severe pulmonary valve stenosis.

The reported average peak systolic velocity in the main pulmonary artery of normal subjects is 57 to 83 cm/s.[131–133] Therefore a threefold to sevenfold increase in peak systolic velocity across the thickened pulmonary valve (200 to 500 cm/s) occurs with an approximate 20 to 100 mm Hg fall in pressure across the valve secondary to the conversion of pressure into kinetic energy (K.E. = $\frac{1}{2}$ pV^2, where K.E. = kinetic energy, p = density of blood, and V = velocity).

Anatomically, the origin of the right pulmonary artery is closer to the pulmonary orifice than the left pulmonary artery. Being nearer to the "dome" of the pulmonary valve, the driving pressure for the flow into the right pulmonary artery is that same pressure in the proximal main pulmonary artery before the jet formed in the thickened valve breaks up. Therefore the pressure recorded in the right pulmonary artery is similar in contour and amplitude to that in the proximal main pulmonary artery. As the jet dissipates in the distal main pulmonary artery and velocity decreases, the kinetic energy component of the total energy decreases and the pressure component increases; the result is a greater mean and peak systolic pressure in the left pulmonary artery.[127] These observations indicate the important role of anatomy of the central pulmonary arteries in regional vascular pressure development and support Chen and colleagues' observation of unequal distribution of pulmonary blood flow in patients with pulmonary valve stenosis, preferentially to the left lung.[134]

As the catheter is withdrawn through the stenotic valve, an abrupt change in the pressure tracing from the low pulmonary arterial pressure to the high-pressure right ventricle is seen. As the stenosis is more severe, the shape of the right ventricular pressure curve becomes more triangular, with a slow rise and descent.[124] In some cases of combined pulmonary valve and infundibular stenosis, two pressure gradients may be found with a characteristic infundibular pressure pulse pattern in severe cases.[125] Because of the high systolic velocity across the narrowed infundibulum, the pressure is decreased owing to the Bernoulli effect. During early systole, both main ventricular and infundibular pressure tracings show a similar initial rise. As blood velocity increases in the outflow tract, the pressure falls there. However, the pressure remains high throughout systole in the main body of the right ventricle. During the remaining portion of systole, the contraction of the hypertrophic infundibular muscle causes a decrease in effective orifice size with subsequent distal increase in velocity and fall in pressure.

The right ventricular end-diastolic pressure may be normal or elevated in patients with severe pulmonary valve stenosis. The right atrial pressure curve usually shows tall A waves in severe obstruction, while in mild-to-moderate stenosis the A wave is frequently normal. A prominent V wave may be present in patients with significant obstruction and secondary tricuspid valve insufficiency. Vogelpoel noted a slow rate of the Y descent with a shallow or absent Y trough in patients with severe infundibular and valvar obstruction, while the Y descent and trough are normal in individuals with mild stenosis.[135]

The normal pulmonary valve area is approximately 2.0 cm^2/m^2 of body surface area. In mild-to-moderate pulmonary valve stenosis, the valve area may range from 1.0 to 2.0 cm^2/m^2. In severe stenosis, the valve area may be calculated to be as low as 0.25 cm^2/m^2 but usually less than 1.0 cm^2/m^2. The presence of associated infundibular stenosis invalidates Gorlin and Gorlin's formula for the calculation of valve area.[42] Assessment of severity of pulmonary valve stenosis requires knowledge of both the pressure gradient and the flow across the valve. A large pressure gradient may be seen in a patient with mild stenosis when the pulmonary flow is high. Conversely, a small gradient may be present in a patient with severe stenosis if the pulmonary flow is low. Hare and co-workers recently demonstrated a simplified formula for the calculation of pulmonary valve area in patients with pulmonary valve stenosis. The simplified formula correlates well with the Gorlin formula.[136]

$$\text{Gorlin formula: PVA } (cm^2) = \frac{CO/HR \times SEP}{C_1 \times C_2 \sqrt{RV - PA}}$$

$$\text{Simplified formula: PVA } (cm^2) = \frac{CO}{\sqrt{RV - PA}}$$

where PVA = pulmonary valve area; CO = cardiac output in milliliters per minute in the Gorlin formula and liters per minute in the simplified formula; HR = heart rate in beats per minute; SEP = systolic ejection period in seconds per beat; C_1 = discharge coefficient with an arbitrary value of 1.0 for the pulmonary valve; C_2 = 44.5 cm/s^2, which is equal to the square root of twice the gravity acceleration; and RV − PA = mean pressure gradient (mm Hg) across the pulmonary valve. The pulmonary valve area is indexed by dividing the calculated valve area from either formula by the body surface area (in square meters).

Muster and co-workers questioned the validity of calculating the pulmonary valve area because blood accelerates across the stenotic valve and the proximal pressure before acceleration and the distal pressure before deceleration are used in the equation.[127] In assessing the severity by using the peak-to-peak systolic pressure difference across the valve, one must question the validity when the Bernoulli effect is so pronounced that the pulmonary arterial curve results in a "valley." A more accurate indicator of severity might be the maximum pressure difference between right ventricle and proximal main pulmonary artery. This would also be more reflective of the Doppler echocardiogram's "instantaneous" peak systolic velocity and calculated gradient.

The measurement of cardiac output during cardiac catheterization is important in evaluating the severity of pulmonary valve stenosis. In our laboratory, the Fick principle is applied using measured oxygen consumption by a "flow-through" technique. It is interesting to note that the data from the U.S. Joint Natural History Study suggested that the most important correlation between peak transvalvular gradient and possible hemodynamic factors influencing the pressure gradient was the heart rate.[75,76] When the pressure gradient is adjusted for heart rate, the inclusion of cardiac output does not improve the accuracy of prediction of severity.

Cotter and colleagues first demonstrated the usefulness of tem-

porary balloon occlusion of an atrial communication in assessing the severity of pulmonary valve stenosis by increasing right ventricular output with a subsequent increase in gradient across the valve.[137]

Exercise Hemodynamics

Measured resting cardiac output in children with pulmonary valve stenosis is usually normal, even in cases of severe obstruction. Several studies using exercise or the infusion of isoproterenol have demonstrated an increase in systolic gradient across the stenotic valve.[138–142] The increase in the rate of right ventricular contraction with subsequent increase in velocity across the obstruction accounts for the pressure gradient increase.[41] Several studies have measured oxygen consumption, oxygen extraction, heart rate, cardiac output, stroke volume, and right ventricular end-diastolic pressure at rest and during exercise in normal children as well as in patients with pulmonary valve stenosis.[142–146]

A study by Krabill and co-workers noted some important differences in exercise hemodynamics between children and adults with pulmonary valve stenosis.[147] Children with mild-to-moderate stenosis usually demonstrated a normal response to exercise, while adults with a similar degree of obstruction often exhibited some hemodynamic abnormalities. Both children and adults with severe stenosis had an abnormal response to exercise, with some notable differences. The most apparent difference was that adults with severe pulmonary valve stenosis have a disproportionately low cardiac index at rest and during exercise when compared to children with similar severity of disease. These adults also had a lower cardiac rate and right ventricular systolic pressure than children with comparable severity but showed the same percentage change from rest to exercise. Stroke index, an indicator of myocardial systolic function, increased significantly with exercise only in children with mild stenosis. Adults with severe stenosis had a lower stroke index at rest and during exercise than adults and children with mild-to-moderate obstruction, but similar to children with severely stenotic valves. Right ventricular end-diastolic pressure was used as an indicator of myocardial diastolic function. Both children and adults with severe stenosis had elevated end-diastolic pressures at rest and an increase in right ventricular end-diastolic pressure with exercise. This abnormal response suggests altered ventricular compliance. Adults with even moderate stenosis also demonstrated an abnormal increase in right ventricular end-diastolic pressure with exercise. In comparable children, the end-diastolic pressure decreased or remained unchanged during exercise, a normal response.[147] These data support the aggressive treatment of moderate-to-severe pulmonary valve stenosis in children, with the hope of avoiding late cardiac dysfunction.

Several other studies have addressed the issue of abnormal cardiac function at rest and with exercise after surgical valvotomy.[148–150] An important difference in younger patients compared to older patients at the time of surgical repair is the reduction of right ventricular end-diastolic pressure and improvement of stroke index at rest and during exercise in children within one year of the operation. This implies that postoperative resolution of muscular hypertrophy is responsible for the improvement seen in children, while myocardial fibrosis explains the lack of improvement in adults.

Classification of Severity

Before proceeding with angiocardiography, clarification of the manner of grading severity of pulmonary valve stenosis is in order. The calculation of pulmonary valve area has several problems, making it unacceptable as an index of severity. The measurement of transvalvular gradient by Doppler echocardiogram and/or cardiac catheterization and the comparison of right ventricular pressure to systemic arterial pressure appear more suitable for determining severity. In our laboratory, *mild* pulmonary valve stenosis is considered to be present if the systolic gradient across the valve is less than 40 mm Hg (particularly in young children) and/or the right ventricular pressure is less than one half the left ventricular pressure. *Moderate* pulmonary valve stenosis is defined as a gradient greater than 40 mm Hg and/or right ventricular pressure greater than one half but less than the left ventricular pressure. *Severe* stenosis is classified as a transvalvular gradient greater than 80 mm Hg and/or right ventricular pressure equal to or greater than left ventricular pressure. These definitions assume a normal cardiac output under resting conditions. It is therefore imperative to measure the cardiac output, especially if the gradient is to be used for management.

Angiocardiography

The introduction of image intensifiers, high-resolution video recorders and monitors, and video disc recording equipment has greatly facilitated the diagnostic and therapeutic interventional techniques for invasive pediatric cardiologists. The use of biplane cineangiocardiography has proved invaluable in identifying the location and assessing the severity of pulmonary stenosis.

Pulmonary valve stenosis is best demonstrated by right ventriculography performed in the standard anteroposterior and lateral projections (Fig. 81–11A, B). To facilitate imaging the leaflets, the anteroposterior camera is rotated approximately 40° to 45° cephalad. Although the pulmonary valve leaflets are seen quite well in the lateral projection, the angled anteroposterior view also allows more detailed imaging of the main pulmonary artery as well as both right and left branches. The stenotic valve leaflets are usually mildly thickened, smooth, and dome in systole. Fused leaflets curl toward the apex of the dome in systole, and a jet of contrast material is seen passing across the valve. In diastole, the leaflets return to a normal position. Although the pulmonary valve annulus is usually normal, in cases of severe stenosis of the newborn or young infant the annulus may be found to be hypoplastic. The main pulmonary artery frequently has poststenotic dilatation with the jet directed along the anterosuperior margin of the artery, extending into the proximal left pulmonary artery. As was stated earlier in the chapter, the degree of poststenotic dilatation does not correlate with the severity of obstruction. A right ventriculogram also allows visualization of tricuspid valve insufficiency if it is present.

The right ventricular morphologic abnormalities secondary to the stenotic valve may also be seen from the right ventriculogram. The trabeculae may be prominent and hypertrophic with a cavity that is usually normal sized, but they may be hypoplastic or even dilated if there is congestive heart failure. The infundibulum may be hypercontractile and hypertrophic, although not displaced. In the lateral projection, the thickened ventricular septum may encroach on the left ventricular outflow tract. The levophase of the right ventriculogram may be of value in assessing pulmonary ve-

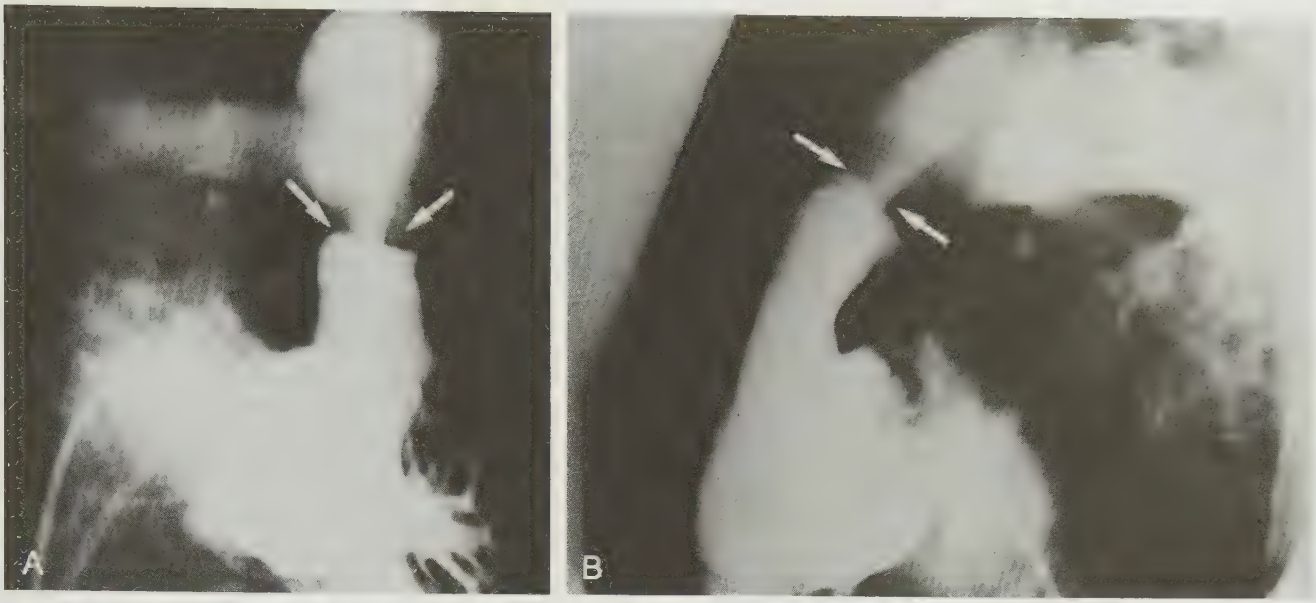

Fig. 81–11. A right ventriculogram in a patient with typical features of moderate pulmonary valve stenosis. (A) Anteroposterior view demonstrating systolic doming of the stenotic leaflets with a "jet" of contrast material noted (see arrows). The infundibulum is widely patent, and the main pulmonary artery is dilated. (B) The lateral projection is also useful in viewing the systolic "jet" that passes through the thickened leaflets as depicted by the arrows.

nous return, presence of an atrial or ventricular septal defect, left ventricular contractility, and presence of a patent ductus arteriosus. However, if the presence of an associated defect causing significant left-to-right shunting is suggested by oximetry, appropriate selective angiograms should be performed. Quantitative right ventricular angiographic measurements in patients with pulmonary valve stenosis and intact ventricular septum have shown that the right and left ventricular functions are usually normal.[151]

Koretzky and associates,[32] and later Jeffrey and associates,[33] characterized the anatomic and angiocardiographic appearance of patients with dysplastic pulmonary valves that distinguish them from the more typical pulmonary valve stenosis. Although the leaflets are not fused, they are extremely thickened with restrictive mobility. The angiogram demonstrates irregular and excessively thickened leaflets that remain deformed and unchanged during the cardiac cycle. The sinuses are narrowed and distorted. One finds that the annulus and the proximal main pulmonary artery are frequently hypoplastic. Systolic doming and poststenotic dilatation are infrequently seen. A report by Schneeweiss and colleagues refuted some of these angiocardiographic criteria for dysplastic pulmonary valve stenosis.[152] In that study, 75% of the patients had poststenotic dilatation, while 33% had a systolic jet. The consistent features found by Schneeweiss and colleagues appeared to be excessive thickening of the valve leaflets (particularly at their edges), a thin base, and little movement of the valve during the cardiac cycle.

The dysplastic pulmonary valve is found frequently in patients with Noonan's syndrome. The levophase of the right ventriculogram in patients with Noonan's syndrome may also be helpful in demonstrating some of the associated abnormalities of the left ventricle.[153] The left ventricle may show eccentric hypertrophy affecting the septum close to the outflow tract, the superior portion of the anterior wall, and/or the diaphragmatic portion of the ventricle.[154] A combined angiographic appearance of the hypertrophy affecting the left ventricle may produce a "ballerina foot" deformity. Hoeffel and co-workers also described cases with dysplastic pulmonary valves and associated supravalve stenosis.[155] Dysplastic pulmonary valve stenosis has also been reported in leopard syndrome and Watson's syndrome.[156,157]

A syndrome of widespread cardiovascular disease associated with pulmonary valve stenosis was described by Becu and co-workers.[158] They pointed out that a thick, tricuspid, relatively immobile pulmonary valve may be only part of a more widespread cardiovascular disease manifested by myocardial dysplasia and necrosis of one or both ventricles, coronary artery occlusion, and a "higgledy-piggledy" aortic wall histology. Myocardial dysfunction at angiography with a dysplastic pulmonary valve and a small, nondistensible ascending aorta should alert the pediatric cardiologist to this pattern of more diffuse cardiovascular abnormalities.

Differential Diagnosis

The diagnosis of pulmonary valve stenosis with intact ventricular septum is usually correctly made if the physician gives careful attention to the physical exam and appropriate use of noninvasive techniques. Most of the cardiac defects that are considered in the differential diagnosis of pulmonary stenosis are discussed more completely in other chapters of this book. Mild pulmonary stenosis must be differentiated from atrial septal defect, pulmonary artery stenosis, ventricular septal defect, idiopathic dilatation of the pulmonary artery, straight back syndrome, mitral valve prolapse, aortic valve stenosis, and innocent pulmonary flow murmurs. If cyanosis is absent and there is moderate-to-severe pulmonary valve stenosis, the diagnosis of ventricular septal defect with or without associated pulmonary stenosis and moderate aortic stenosis must be entertained. The major congenital heart defects that mimic

severe pulmonary valve stenosis with intact ventricular septum presenting with cyanosis are tetralogy of Fallot and pulmonary valve atresia with intact septum. Ebstein's anomaly of the tricuspid valve may sometimes present a confusing clinical picture. We will also review several systemic disease processes that involve the pulmonary valve that must be considered from a diagnostic standpoint when a patient presents with clinical features of pulmonary stenosis.

Atrial Septal Defect

The moderate-to-large secundum atrial septal defect is unlikely to be confused with pulmonary stenosis; atrial septal defect is characterized by the prominent right ventricular impulse, wide and fixed splitting of S_2, mid-diastolic flow rumble over the tricuspid valve, and increased pulmonary vascular markings on chest roentgenogram. However, small defects may be more difficult to differentiate from pulmonary valve stenosis. The systolic ejection click of valve stenosis may be helpful, but an aneurysm of the atrial septum may cause a systolic click. Frequently, echocardiography is necessary to distinguish between the two abnormalities. Clinical and laboratory features of atrial septal defect are discussed in Chapter 60.

Pulmonary Artery Stenosis

Pulmonary artery stenosis is commonly associated with mild pulmonary valve stenosis, and the physical signs are similar. If there are bilateral stenoses, the widely transmitted systolic ejection murmur to the back and lateral lung fields helps to differentiate this abnormality. The murmurs of pulmonary artery stenosis are also characteristically mid- to late systolic in timing. If there are signs of rubella, a family history of siblings with pulmonary stenosis, or intrahepatic biliary dysgenesis, then the diagnosis of pulmonary artery stenosis should be suspected, since these are frequently associated with pulmonary stenosis.

Ventricular Septal Defect

Some infants with pulmonary valve stenosis have a peculiar, low position of the systolic murmur along the left sternal border that may be confused with ventricular septal defect. This is especially true with small defects of the ventricular septum, since the murmur is often diamond-shaped.[163] Vogelpoel and associates demonstrated that the administration of amyl nitrate decreases the length and intensity of the murmur of ventricular septal defect but accentuates the murmur of pulmonary valve stenosis.[164] Although the murmur accompanying aneurysmal transformation of ventricular septal defect may be confused with infundibular stenosis or acyanotic tetralogy of Fallot, it is usually distinct from pulmonary valve stenosis.[165] Supracristal ventricular septal defects (type I) may be heard at the upper or middle left sternal border and may create a difficulty in differentiation from pulmonary stenosis.

In moderate-to-large ventricular septal defects, the murmur is typically holosystolic and located along the left lower sternal border. There is no ejection click, and the second sound depends upon the pulmonary vascular resistance. However, an aneurysm of the ventricular septum with ventricular septal defect can cause a click. There is frequently a mid-diastolic flow rumble located over the mitral valve area with a ventricular septal defect if the left-to-right shunt is larger than 2:1. The chest roentgenogram shows cardiomegaly with increased pulmonary vascular markings, and the electrocardiogram demonstrates left or combined ventricular hypertrophy with ventricular septal defect. Echocardiography easily distinguishes these two congenital heart defects.

Idiopathic Dilatation of the Pulmonary Artery

Clinically, idiopathic dilatation of the pulmonary artery is quite similar to mild pulmonary valve stenosis, since a pulmonary systolic ejection click, a widely split second heart sound, and radiographic features of dilated main pulmonary trunk are also present in this benign condition. Although a systolic murmur may be present, it is quite soft in comparison to pulmonary valve stenosis. The echocardiogram demonstrates a normal-appearing pulmonary valve with normal Doppler flow and should help in differentiating these two conditions. Cases of idiopathic dilatation of the pulmonary artery that were diagnosed clinically in the era before echocardiography have been reclassified as mild pulmonary valve stenosis on more recent followup with Doppler and two-dimensional echocardiographic evaluation. This may be part of the continuum of mild pulmonary stenosis rather than a discrete entity.

Straight Back Syndrome

This syndrome described by Doty may be confused with mild pulmonary valve stenosis, since both have a pulmonary systolic ejection murmur and split second sound. Usually, there is not a systolic ejection click.[166–169] The presence of an associated pectus excavatum and typical chest radiographic features should alert the physician to this condition. Echocardiography demonstrates normal cardiac anatomy.

Mitral Valve Prolapse

Unusual cases of mitral prolapse may present with a nonejection systolic click and systolic murmur located at the middle and upper left sternal border and may be confused with pulmonary stenosis. The unusual transmission of these auscultatory findings has been attributed to the prolapse of the medial leaflet and to the direction of the mitral regurgitant flow toward the more anteriorly located atrial appendage. Echocardiography is a more precise means to diagnose this entity. Mitral valve prolapse is discussed in greater detail in Chapter 114 of this book.

Aortic Valve Stenosis

In young infants, aortic stenosis is occasionally difficult to distinguish from pulmonary stenosis by physical examination alone. The location of the murmur may actually be heard best along the left rather than the right sternal border. The systolic ejection click may be heard diffusely rather than being confined to the apex. The electrocardiogram in both conditions in infancy frequently shows right ventricular hypertrophy. The echocardiogram distinguishes between these two conditions. Occasionally, combined pulmonary and aortic stenoses are present, and the echocardiogram establishes these diagnoses.[170–172] Aortic stenosis is discussed in greater detail in Chapter 79.

Innocent Murmurs

Although their location may be similar, innocent murmurs are usually shorter in duration, softer in intensity, and unaccompanied by a systolic ejection click. Innocent murmurs frequently are low frequency and vibratory in quality with a normally split second heart sound. Trivial degrees of pulmonary stenosis may be indis-

tinguishable from a functional murmur by auscultation. Greater detail on confident differentiation of the functional murmurs is found in Chapter 109.

Tetralogy of Fallot

Cyanotic patients with severe pulmonary valve stenosis and intact ventricular septum must be distinguished from those with tetralogy of Fallot. Typically, the cyanosis is more intense with tetralogy of Fallot. The systolic ejection murmur frequently ends before the single second heart sound in tetralogy of Fallot. An ejection click is often present in the tetralogy of Fallot patient with a greatly dilated aorta but in general is a clue to valvular pulmonary stenosis. The chest roentgenogram usually demonstrates a normal cardiac size, an uptilted right ventricular apex, a deficient pulmonary artery segment, and decreased pulmonary vascular markings in tetralogy of Fallot. The presence of a right aortic arch should strongly alert the pediatric cardiologist to the possibility of tetralogy of Fallot. The electrocardiogram usually has moderate right ventricular hypertrophy in contrast to the severe right ventricular hypertrophy associated with critical pulmonary valve stenosis. The use of echocardiography has allowed the physician to easily diagnose these two conditions noninvasively and expedite appropriate therapy. Tetralogy of Fallot is discussed more completely in Chapter 63.

Pulmonary Valve Atresia with Intact Ventricular Septum

It is not surprising that pulmonary valve atresia with intact ventricular septum may present with features similar to those of severe pulmonary valve stenosis, i.e., cyanosis and congestive heart failure. The pathophysiology is nearly identical, particularly in newborns with critical obstructive stenosis, tricuspid insufficiency, and right-to-left atrial shunting. Both conditions require patency of the ductus arteriosus for adequate pulmonary blood flow. In infants with a hypoplastic right ventricle, the electrocardiogram may demonstrate predominant left ventricular voltage. Radiographically, there are findings similar to critical pulmonary stenosis in infants with cardiomegaly due to a dilated right atrium, decreased pulmonary vascular markings, and a left aortic arch. The echocardiogram in experienced hands usually distinguishes between these two conditions by demonstrating prograde flow through the severely stenotic pulmonary valve. Accurate noninvasive diagnosis allows the pediatric cardiologist to plan for balloon dilation of the critically stenotic pulmonary valve while expediting the readiness of the operating room for the infant with pulmonary valve atresia and intact septum.

Ebstein's Anomaly of the Tricuspid Valve

Ebstein's anomaly occasionally presents as a cyanotic infant with a systolic murmur of moderate intensity over the middle to lower sternal border associated with an active precordium. Chest roentgenogram reveals massive cardiomegaly and decreased pulmonary vascular markings. The electrocardiogram is quite different from critical pulmonary stenosis in these patients, demonstrating reduced voltage, right bundle branch block, and right atrial enlargement. The echocardiogram demonstrates classic features of an inferiorly displaced septal leaflet and long redundant anterior leaflet of the tricuspid valve. Further discussion of this malformation is found in Chapter 68.

There are a number of other cyanotic congenital heart defects that one has to consider in the differential diagnosis of severe pulmonary valve stenosis with right-to-left atrial shunting. A percentage of these defects may have pulmonary stenosis as an associated feature. However, the expert use of two-dimensional, Doppler, and color flow echocardiography should permit differentiation of all of these conditions and allow for prompt and appropriate therapy.

Systemic Diseases Associated with Pulmonary Stenosis

Myocarditis, glycogen storage disease, and left ventricular obstructive disease have been reported to produce infundibular and valvar pulmonary stenosis.[173–177] Tophaceous deposits have been demonstrated in the pulmonary valve secondary to gout.[178] Gottsegen and colleagues[179] and Catton and colleagues[180] reported that right ventricular or pulmonary valvar myxomata may closely resemble severe isolated pulmonary valve stenosis. Two-dimensional and Doppler echocardiography have been used to diagnose right ventricular outflow obstruction secondary to external compression from an anterior mediastinal tumor.[181,182] Intracardiac goiter has also been implicated as a cause of right ventricular outflow tract obstruction.[183] Neurofibromatosis, or von Recklinghausen's disease, has been reported to cause both infundibular and valvar pulmonary stenosis.[184–186] Pulmonary valve and artery stenosis have been reported in multiple lentigines syndrome, or leopard syndrome.[156,187] Watson described a syndrome of patients with pulmonary stenosis, cafe-au-lait spots, and dull intelligence.[157]

Carcinoid disease of the bowel has been associated with endocardial fibrosis of the right ventricle with infiltration of the pulmonary and tricuspid valves leading to stenosis of variable severity.[188] Symptoms including abdominal pain, diarrhea, weight loss, flushing, and generalized telangiectasia have been attributed to excessive release of serotonin. Carcinoid occurs in older children or adults.

It is worthwhile to reemphasize that Noonan's syndrome is associated with congenital heart disease in 50% of the cases, usually dysplastic pulmonary valve stenosis.[17,29] Hypertrophic cardiomyopathy with or without pulmonary stenosis has been reported in 25% of cases.[189] These patients may present a problem in determining the severity of obstruction from physical exam. The ejection click is usually absent, and the systolic murmur may be of low intensity, despite the severity. An atypical electrocardiogram showing left axis deviation may be found. It is wise to investigate children suspected of having Noonan's syndrome quite thoroughly as well as inquiring about other family members.

Natural History

Most pediatric cardiologists would agree that mild pulmonary valve stenosis has a benign clinical course and requires no therapy. No deaths were reported from a study of 214 patients with mild stenosis in a four- to eight-year followup.[190] In the U.S. Joint Study of the Natural History of Congenital Heart Defects, among 261 patients treated medically, only three with initial gradients of less than 40 mm Hg had gradients of 60 mm Hg or more over a period of four to eight years.[76] The actual mean pulmonary valve gradient in this group of patients was unchanged or decreased over the years of followup. Furthermore, catheterization studies have shown normal cardiac output at rest and during exercise with a completely normal hemodynamic response to exercise in patients with mild pulmonary valve stenosis. One study has actually doc-

umented a decrease in right ventricular systolic pressure and transvalvular gradient with time that might be attributed to an increase in the stenotic pulmonary orifice size as the child grows.[191]

There is controversy regarding the clinical course and prognosis of children with moderate pulmonary valve stenosis.[192,193] In Jonson and associates' study of 21 asymptomatic adult patients with pulmonary valve stenosis, no cardiac symptoms or complications developed over a period of 15 years.[194] Data from most centers as well as the information from the U.S. Joint Study suggest that infants and children with moderate stenosis, especially those with severe obstruction, may develop progressively higher transvalvular gradients.[76,190] A more recent study by Lange and co-workers demonstrated a significant gradient increase of 8.6 mm Hg/yr in a followup over 2 to 12 years in infants and children with an initial systolic gradient of greater than 50 mm Hg. This was quite different from the −0.6 mm Hg/yr gradient decline in patients with an initial pulmonary valve gradient of less than 50 mm Hg.[195] Krabill and associates' exercise data in patients with moderate pulmonary valve stenosis reviewed earlier in this chapter implied reduced systolic and diastolic function of the right ventricle.[147] Although prediction of the clinical course of moderate pulmonary valve stenosis is difficult, newer data seem to support more aggressive therapy in these individuals. This is especially true since balloon pulmonary valvuloplasty with low risk and high efficacy has become available.

In the U.S. Joint Study of 261 patients treated medically, there was no improvement in severe obstruction with gradients in excess of 80 mm Hg.[76] An increase in gradient is possible during periods of rapid growth, i.e., infancy and adolescence. Hemodynamic deterioration can occur by three mechanisms:

1) As the child grows, the orifice of the stenotic pulmonary valve can remain constant. Danilowicz and colleagues found that in 17 of 32 infants with pulmonary stenosis, the pulmonary valve area decreased with age.[196] In older children with pulmonary stenosis, serial cardiac catheterizations have shown that the pulmonary valve area increased proportionally to the increase in body size and cardiac output.[197,198]
2) Right ventricular myocardial function may be impaired by the development of fibrosis or hypertrophy. In the 64 children studied by Moller and co-workers, those with severe pulmonary stenosis had evidence of myocardial dysfunction believed to be a result of myocardial hypertrophy in the majority and myocardial fibrosis in three children.[139] Adults with severe obstruction had a lower cardiac index at rest and during exercise than any other group of adults or children with pulmonary stenosis.[147]
3) Infundibular hypertrophy may develop, causing a secondary site of right ventricular outflow tract obstruction.[196,199]

Although the development of symptoms during the first two years of life is associated with severe obstruction, one should not rely on symptoms being present to establish the severity of disease.[76,200] In the U.S. Joint Study, none of the medically treated children younger than 12 years of age with pulmonary valve gradients greater than 80 mm Hg had symptoms, although the majority had radiographic or electrocardiographic abnormalities.[76] In another series, 33% of patients with right ventricular pressure greater than 120 mm Hg demonstrated symptoms.[190] Serial catheterization data in patients with severe pulmonary valve stenosis are lacking, since the majority of these patients are treated. However, clinical and electrocardiographic data suggest a progression in severity of obstruction. Regardless of the degree of elevated right ventricular pressure, the presence of congestive heart failure is an ominous sign and requires immediate therapy.

Sudden death has been reported in children without apparent relation to unusual strenuous activity.[65,66,201,202] In the current era, sudden death in children is rare, and most deaths occur in newborns with critical pulmonary valve stenosis.[2,45,76,203] Cyanosis is very common in the severe form of this disease in young infants, being present in 50% of those with gradients in excess of 80 mm Hg. The presence of hypoxic spells has been recognized as a grave prognostic sign.[204]

Abbott described two cases of infective endocarditis in 25 autopsies of patients with pulmonary valve stenosis.[205] Abrahams reported a relatively high incidence of endocarditis (3% of their cases).[1] In the U.S. Joint Study, only 2 out of 598 patients with pulmonary stenosis had a history of infective endocarditis.[76] Infective endocarditis seems to constitute a relatively minor risk to individuals with pulmonary valve stenosis and intact septum regardless of medical or surgical treatment. Appropriate antibiotic prophylaxis should be administered before any indicated procedure.[206]

Treatment

Medical

Children with mild pulmonary valve stenosis do not require surgical or balloon valvuloplasty intervention. Cardiac catheterization is unnecessary unless the patient is symptomatic or noninvasive testing suggests more obstruction than is evident from clinical examination. These patients are generally followed as outpatients every one to two years with electrocardiogram and echocardiogram to assess changes in severity. There should be no restriction of physical activity. Infective endocarditis prophylaxis is required for all procedures indicated by the American Heart Association.[206]

The treatment of moderate pulmonary valve stenosis is more controversial. Certainly, if these patients are symptomatic, treatment is required. However, if the patients are asymptomatic, the question of therapy is more uncertain. Before the development of balloon pulmonary valvuloplasty, most pediatric cardiologists hesitated to recommend surgical valvotomy in these asymptomatic patients. Yet most physicians were concerned that the long-term right ventricular hypertrophy might lead to functional impairment of the myocardium later in life. Recent studies tend to substantiate these concerns in adults with pulmonary valve stenosis.[147] Therefore we have been more aggressive in the treatment of patients with moderate or moderate-to-severe obstruction. Recommendations depend upon the individual's size, age, and noninvasive test results. Infants and younger children with Doppler-estimated systolic gradients in excess of 40 mm Hg and/or evidence of right ventricular hypertrophy currently undergo cardiac catheterization for possible balloon pulmonary valvuloplasty at our center. Older children with estimated transvalvular gradients of greater than 50 mm Hg and/or right ventricular hypertrophy undergo catheterization with anticipated balloon valvuloplasty.

Untreated infants and young children with moderate pulmonary valve stenosis may need to be seen twice a year as outpatients to evaluate for progression of the disease. Older children and adults

should be seen on a yearly basis with appropriate tests. Exercise studies may be helpful in older individuals to unmask hemodynamic abnormalities. Appropriate infective endocarditis prophylaxis is recommended. If a physician is restricting physical activity in an untreated child on the basis of moderate pulmonary valve stenosis, then balloon valvuloplasty should be performed.

Asymptomatic patients with severe pulmonary valve stenosis should have hemodynamic and interventional cardiac catheterization performed as a semielective procedure. Symptomatic newborns and infants with severe or critical obstruction require immediate treatment. In infants with evidence of right-sided congestive failure and inadequate pulmonary blood flow, the administration of prostaglandin E_1 (PGE_1) infusion intravenously may be life saving by providing adequate pulmonary blood flow through the patent ductus arteriosus. The dose of PGE_1 ranges from 0.05 to 0.10 μg/kg/min with special care to observe for apnea and attention to the possible need for endotracheal intubation. In addition, furosemide (1 mg/kg/dose) and digoxin (total dose of 40 μg/kg to be divided appropriately) may improve signs of congestive heart failure temporarily. However, the infant should be stabilized as quickly as possible and proceed to the cardiac catheterization laboratory for balloon pulmonary valvuloplasty. We routinely alert the pediatric cardiovascular surgeon to the possibility of surgery in case the balloon dilation is unsuccessful. The infusion of PGE_1 is continued during and after the procedure to ensure adequate pulmonary blood flow. The dosage of the medication is gradually reduced and discontinued while the patient's clinical condition and systemic oxygen saturations are observed. The clinical course and prognosis in these infants are variable depending on their clinical condition before ballooning, the degree of tricuspid valve insufficiency, the amount of residual pulmonary valve insufficiency, and, perhaps most important, the size and function of the right ventricle. Followup clinic visits and studies depend upon the clinical status but usually occur every two to three months during the first year of life and one to two times a year thereafter. Again infective endocarditis prophylaxis is important.

Balloon Pulmonary Valvuloplasty

Percutaneous, transluminal balloon angioplasty has been used in the treatment of adults with stenoses of coronary and peripheral arteries since 1976.[207–210] In 1980, the first successful balloon valvuloplasty for congenital pulmonary valve stenosis was performed on Rumbo, an English bulldog, by Kan.[211] Two years later, Kan and co-workers reported the success of this new procedure in an eight-year-old asymptomatic patient with pulmonary valve stenosis.[212] Later, Lababidi and Wu[213] and Kan and co-workers[214] reported their successes in the application of balloon valvuloplasty in children with moderate-to-severe congenital pulmonary valve stenosis. This was the beginning of an explosion of reports of success using this new technique in children and adults with congenital stenoses of all cardiac valves, conduit valves, pulmonary arteries, and coarctation of the aorta.[215–230] The pediatric interventional cardiac catheterization laboratory had begun and added a stimulating new aspect to the management of congenital heart disease that was comparable to the advent of echocardiography in the 1970s.

The physical properties governing balloon angioplasty depend on transmission of a controlled radial force through a rigid balloon.[231] The characteristics of the stenotic tissue determine the effectiveness of the dilation process. Although Semb and co-workers had relieved pulmonary valve stenosis by pulling a carbon dioxide–filled balloon from the pulmonary artery to the right ventricle, this technique had the inherent dangers of avulsion of the valve leaflets.[232] The hypothesis of using transluminal balloon dilation of the stenotic valve as an alternative to surgery was based on several observations: 1) the surgical success of relieving pulmonary valve stenosis by using inflow occlusion and manual dilation techniques, 2) the ability to construct polyethylene balloons of almost any size in which high pressure can be applied without overdistension of the balloon, and 3) the ability of the right ventricle to adequately function after surgical valvectomy.[233] The initial investigators felt that the mechanism of dilation was rupture of valve tissue.[212,213] Therefore, the balloon diameter was chosen not to exceed the angiographically measured pulmonary valve annulus diameter, and high inflation pressures, up to 120 psi (8 atmospheres), were used. Since the early studies, there have been significant improvements in catheter design, in balloon material, and in the actual technique of performing the valvuloplasty procedure.[234–239] With unoperated, typical pulmonary valve stenosis, it was demonstrated that balloons 20 to 40% larger than the angiographically measured pulmonary valve annulus were both safe and more effective.[235] The predilation average systolic gradient of 65 mm Hg was reduced to a mean valvular gradient of 16 mm Hg, a 74% reduction. The use of oversized balloons allowed less inflation pressure to be applied, usually only 4 to 6 atmospheres. This observation is in accordance with the law of Laplace, which states that force is proportional to diameter times pressure.

The single, oversized balloon technique worked well when the pulmonary valve annulus was less than 20 mm in diameter. However, it became apparent that a double-balloon technique would be necessary for adequate relief of pulmonary valve stenosis in larger individuals.[235–237] In selecting the proper size of the two balloons, the reader is referred to Radtke and colleagues' article,[235] and to the part of this book that covers interventional cardiology (Chapter 130). The double-balloon technique has an advantage of "venting" the right ventricle during peak inflation because of the elliptical geometry. The efficacy was apparent with an average reduction in peak systolic pressure gradient from 104 mm Hg before ballooning to 24 mm Hg after balloon dilation.[237] The technique has also been shown to be quite safe. Several disadvantages of the technique are the additional time of inserting and positioning two balloon catheters, the introduction of a large-diameter catheter into both femoral veins, and the additional help required to inflate and position both balloons at the same time. However, since the largest single-balloon diameter is 25 mm at present, the double-balloon technique is necessary to provide adequate relief of obstruction in patients with a pulmonary valve annulus diameter greater than 20 mm. Recent reports from Switzerland and the Netherlands have described two experimental catheter designs with potential benefits using a trefoil balloon and a triple-lumen balloon, respectively.[238,239] Both designs allow transvalvular prograde flow during balloon inflation and have added cross-sectional area because of their configuration. The future certainly appears bright for improved catheter and balloon design for the pediatric cardiologist.

Studies have described the pulmonary valve morphology after balloon dilation for valve stenosis.[240–242] Balloon pulmonary val-

vuloplasty produced relief of obstruction by commissural splitting in patients with the more common and typical thin, doming valve. Usually, only one commissure was opened. When significant infundibular obstruction accompanied pulmonary valve stenosis, the risk of cusp avulsion was higher.[213,240] When the commissures were poorly formed with extensive valvar fibrosis, cusp tearing was more likely to occur. The pulmonary valve morphology in dysplastic valve disease is important. It should come as no surprise that the results of balloon dilation for dysplastic pulmonary valve stenosis are poor.[214,235,242,243] Despite the use of oversized balloons, no relief of obstruction occurred. As a matter of fact, several patients actually had an increase in transvalvular gradient after attempts to balloon-dilate the dysplastic valves.[243] The causes of valvuloplasty failure in these patients include not only the myxomatous, obstructive valve tissue with unfused commissures, but also a hypoplastic main pulmonary artery despite a near-normal-sized valve annulus. In this group of patients, surgical valvectomy remains the treatment of choice.

The risks of percutaneous transluminal balloon pulmonary valvuloplasty are low. We are not aware of deaths reported during this procedure for isolated pulmonary valve stenosis. During the peak inflation or early deflation portion of the procedure, sinus bradycardia and arrhythmias have been noted. Arrhythmias have consisted of premature ventricular contractions, nonsustained ventricular tachycardia, accelerated junctional rhythm, advanced atrioventricular block, and right bundle branch block. Some physicians administer atropine prior to the balloon inflation to minimize the bradycardia. Henry and associates reported an unusual right ventricular pulsus alternans pattern during acute increase in afterload occurring during balloon pulmonary valvuloplasty. The pattern resolved spontaneously.[244] With the use of double balloons or perhaps the newer trefoil or triple-lumen balloons, the incidence of these side effects may diminish.

With the use of proper-sized balloons, pulmonary valve annulus rupture has not been reported. The incidence of residual mild pulmonary insufficiency after balloon valvuloplasty varied from 13 to 20%.[222,235,241] The use of Doppler echocardiography and color flow mapping may increase the detection of pulmonary insufficiency, but this low percentage compares favorably to the 57 to 70% incidence after surgical valvotomy.[76,245] Infundibular spasm has been reported after percutaneous balloon dilation of the stenotic pulmonary valve and after surgical valvotomy (Fig. 81–12A, B).[213,214,221,235,237,246] Propranolol was successfully used for some patients with acutely reduced right ventricular output. However, the role of beta-blocker therapy for infundibular narrowing after relief of the transvalvular gradient is still uncertain. It appears that the secondary infundibular hypertrophy and narrowing are transient. Fontes and co-workers recently reported complete regression of the right ventricular infundibular hypertrophy approximately ten months after balloon pulmonary valvuloplasty in patients with suprasystemic right ventricular pressure.[247] Another potential complication from balloon valvuloplasty is femoral venous thrombosis or intimal damage of the vessel.

In any patient being considered for pulmonary balloon valvuloplasty, we perform complete echocardiographic studies. Special attention is given to obtain a continuous-wave Doppler pulmonary valve velocity while the patient is resting quietly or sedated. We have also found an accurate correlation of the balloon diameter required and the pulmonary annulus measurement obtained from the parasternal right ventricular outflow view on the two-dimensional echocardiogram (Fig. 81–13).[248] If the annulus measurement is made at the base of cusps during systole and from the middle of the anterior to posterior walls (rather than inside the lumen), then the diameter of the balloon necessary for successful dilation equals the echo-derived measurement (Fig. 81–14). During catheterization, standard right and left heart resting hemodynamics are obtained, including measurement of cardiac output by Fick technique. Slow pullback pressure recordings are obtained by using an end-hole catheter. Next, a selective right ventricular angiocardiogram is performed with the anteroposterior camera cranially angulated at 40° and a straight lateral projection. We then repeat the measurements of the right ventricular pressure and transvalvular gradient after angiograms. Calibration grids are recorded and used to measure the pulmonary valve annulus from the angiogram (Fig. 81–15A, B). Others have used calibrated marker catheters for this purpose. By multiplying this measurement by a factor of 1.3, the annulus diameter obtained by echocardiography is usually equalled. An end-hole catheter is repositioned into the distal left pulmonary artery, an appropriate exchange guidewire is placed through the catheter into the left pulmonary artery, and the catheter is withdrawn. While the technician is flushing the balloon catheter with diluted contrast solution (20%) to avoid air within the balloon, a second percutaneous femoral vein catheter is inserted and placed into the right ventricle for pressure measurement during the balloon dilation procedure. The balloon catheter is then advanced over the exchange guidewire, with care taken that the wire remains in the distal left pulmonary artery. Pepine and colleagues observed that the guidewire remaining in the pulmonary artery lessened the risk of pulmonary artery perforation during either catheter advancement or balloon inflation.[249] After the balloon catheter is positioned where the midportion of the balloon coincides with the stenotic pulmonary valve, the balloon is inflated rapidly under fluoroscopy using a hand-held manometer until the "hourglass" waist from the stenotic valve disappears or until the maximum recommended atmospheric pressure is reached (Fig. 81–16A, B). Rapid deflation is performed (total inflation–deflation time less than 7 seconds), and the entire procedure is repeated with repositioning of the balloon catheter as needed or replacement of the catheter with a larger balloon if indicated. Right ventricular and systemic arterial pressures are constantly monitored throughout the procedure. After balloon valvuloplasty has been completed, the cardiac output and transvalvular pressure gradient measurements are repeated (Figs. 81–17 and 81–18). Finally, a repeat right ventricular angiogram is performed. We then routinely perform a postvalvuloplasty two-dimensional and Doppler echocardiogram while in the catheterization laboratory or soon after the patient has been transferred for recovery (Fig. 81–19A, B). A reevaluation of the patient's estimated transvalvular gradient and assessment for pulmonary insufficiency is made. We also repeat an electrocardiogram to assess for any acute changes after the valvuloplasty procedure. Usually, the patient is ready to be discharged on the morning after the procedure. Although we do not routinely have surgical "standby" during the balloon dilation, a precatheterization type and crossmatch for possible blood transfusion has been obtained. In the case of newborns or young infants with critical pulmonary valve stenosis, we do alert our surgeons before the case is started. In addition, we agree that graduated sequential balloon dilation as described by Ali Khan

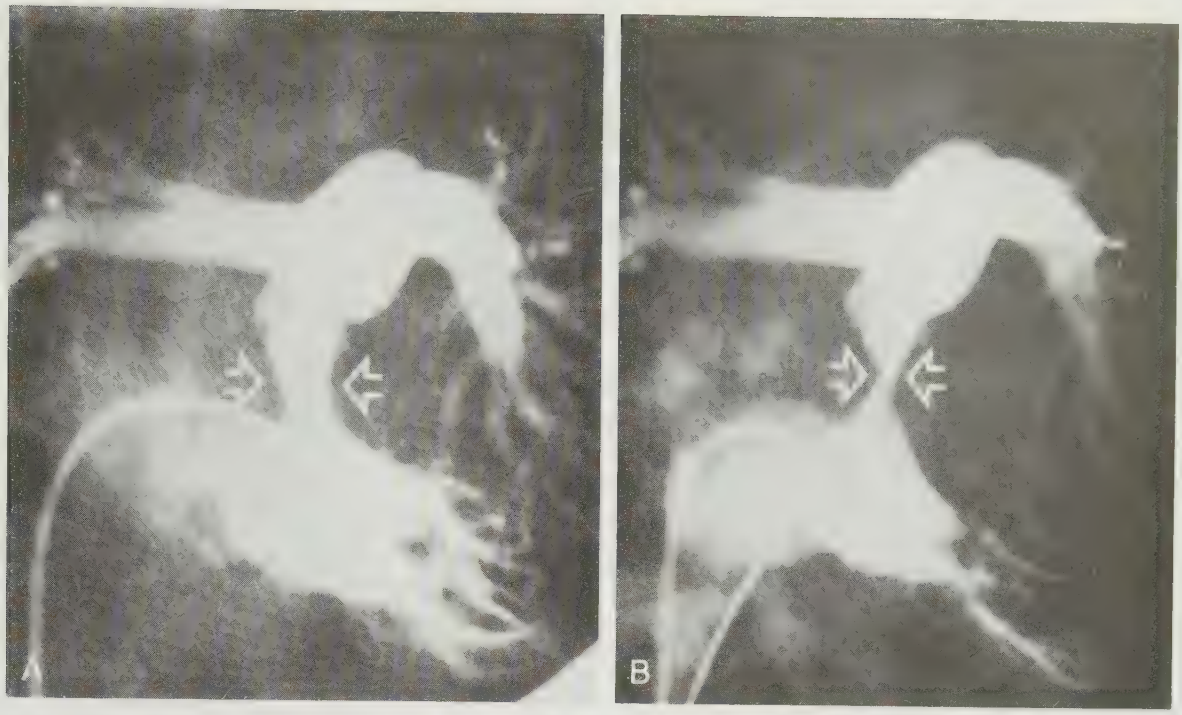

Fig. 81–12. A right ventriculogram in an infant undergoing balloon pulmonary valvuloplasty for severe pulmonary valve stenosis with suprasystemic right ventricular systolic pressure. (A) Preballooning: An anteroposterior projection with 40° cranial angulation allowed visualization of the mildly hypertrophic and narrowed infundibulum (arrows). The angiocardiogram also demonstrated systolic doming of the pulmonary valve with poststenotic dilatation. (B) Postballooning: A repeat angiocardiogram demonstrates severe infundibular narrowing that has significantly increased since the valvuloplasty procedure (arrows). This secondary obstruction was transient with evidence of improvement over several weeks. No treatment with beta-blocker medication was necessary.

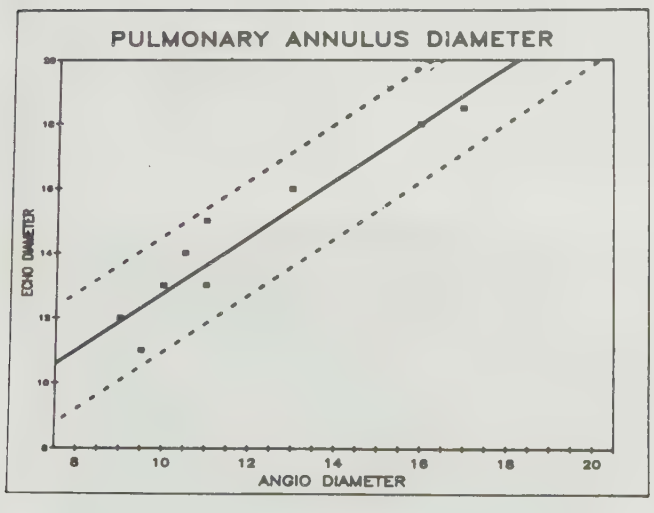

Fig. 81–13. A graph from our laboratory demonstrating the relationship between pulmonary annulus diameter measured from two-dimensional echocardiography and the diameter measured by angiography. As a rule, the two-dimensional echocardiographic measurement is 1.2 to 1.3 times the angiographic measurement. Since a balloon diameter 1.2 to 1.3 times the annulus measured from angiography is frequently chosen, the two-dimensional echo appears to be an accurate method of predicting the proper balloon size for pulmonary valvuloplasty.

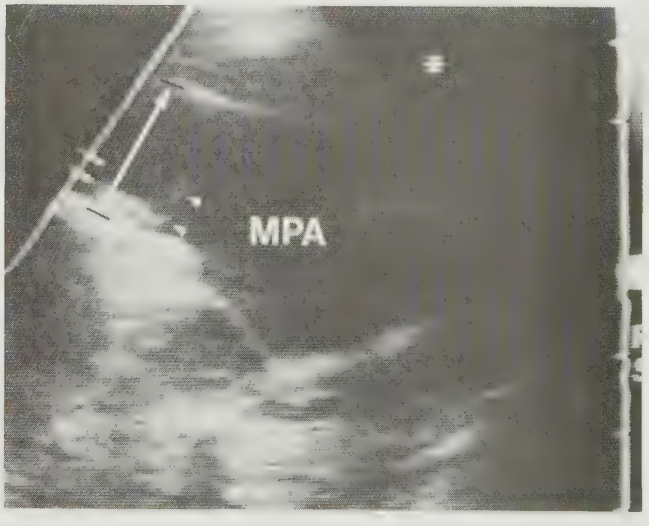

Fig. 81–14. A two-dimensional echocardiogram obtained from the parasternal right ventricular outflow tract view. The pulmonary valve annulus is measured at the base of the leaflets from the middle of the anterior and posterior walls, as depicted by the long arrow between the black markers. This annular diameter is predictive of the necessary balloon size for successful valvuloplasty. The pulmonary valve leaflets dome in systole (the two small arrowheads), and the main pulmonary artery (MPA) is dilated.

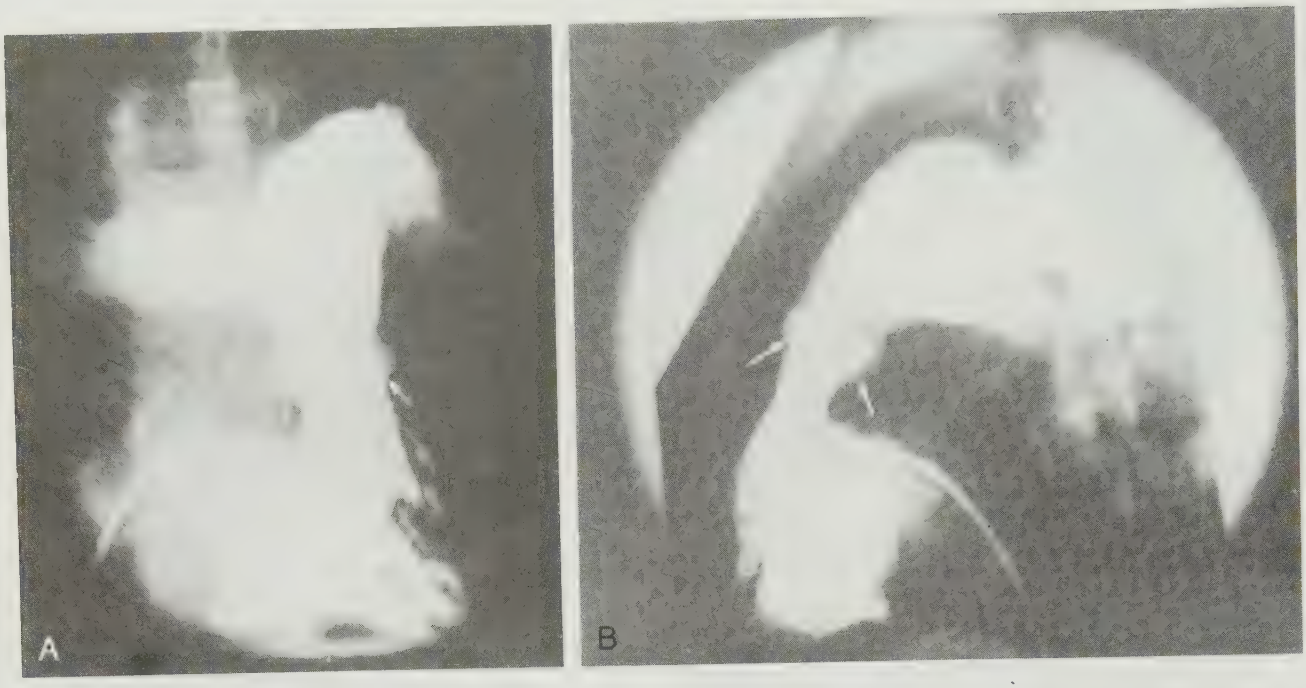

Fig. 81–15. A right ventriculogram used for measurement of the pulmonary valve annulus diameter. (A) The anteroposterior view with the base of the pulmonary leaflets depicted by arrows. The distance between the two arrows is the angiographic annular diameter. This value (in millimeters) times 1.2 to 1.3 usually equals the proper balloon size for successful valvuloplasty. (B) The lateral view also is helpful in measuring the pulmonary valve annulus (distance between the arrows).

and co-workers is frequently necessary in the infants with critical obstruction (Fig. 81–20a, b, c, d).[250]

Long-term followup of patients who have had balloon pulmonary valvuloplasty is still limited. Several authors have demonstrated persistent relief of right ventricular hypertension for up to three years.[213,214,220,235,235] In addition, improvement of both right ventricular hypertrophy on electrocardiogram and a lower-intensity systolic murmur are common. The benefits of the procedure are many. The procedure can be performed during hemodynamic cardiac catheterization and eliminates the need for general anesthesia and open heart surgery. Valvuloplasty eliminates the exposure to blood products. It reduces the hospitalization period from 7 to 10 days to less than 48 hours in most instances with a reduction in cost. It can also be performed in children with other major medical illness that might make them poor anesthetic or operative risks. There is the additional benefit of no surgical scar, cosmetic or psychologic, and the procedure can be repeated if necessary.

Although the long-term results are still unknown, the current data strongly support the statement that percutaneous transluminal balloon valvuloplasty is the treatment of choice for patients with

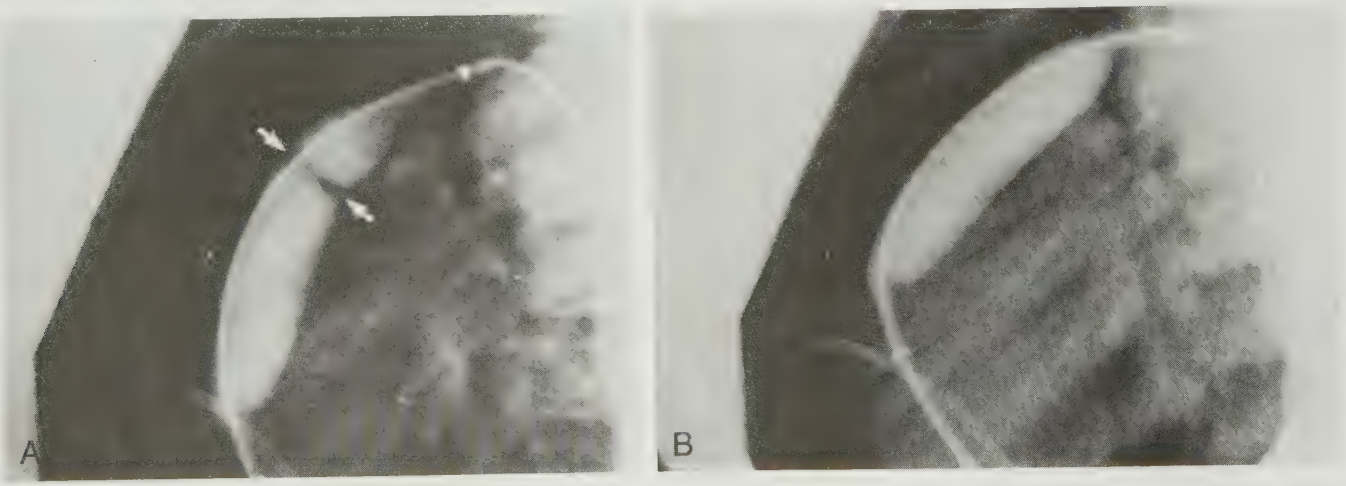

Fig. 81–16. Proper positioning of the balloon catheter for pulmonary valvuloplasty using the lateral view under fluoroscopy. (A) A guidewire is passing through the catheter from the right ventricular outflow tract into the left pulmonary artery. The balloon is inflated with diluted contrast (20%) until a "waist" is seen that corresponds to the stenotic valve leaflets (arrows). Proper positioning of the catheter is performed in an attempt to maintain the waist at the midportion of the balloon. In this case, the waist is toward the distal one third of the balloon. (B) The balloon has been repositioned more distally and completely inflated by using a handheld manometer. Note that the hourglass waist has completely disappeared.

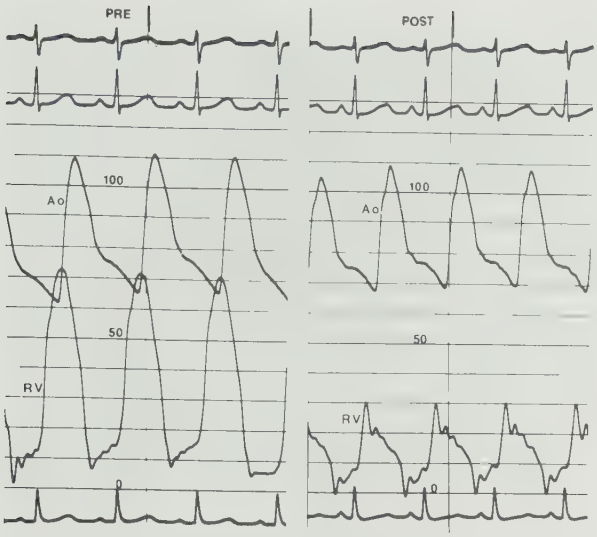

Fig. 81–17. Pressure recordings obtained at cardiac catheterization before and after balloon valvuloplasty for moderate pulmonary valve stenosis. In the left panel, the right ventricular (RV) systolic pressure is somewhat greater than 70 mm Hg before balloon valvuloplasty (PRE). Note the triangular appearance of the RV pressure curve, which indicates significant stenosis. After valvuloplasty (POST), the RV systolic pressure decreased to 30 mm Hg with a completely normal pressure curve. Aortic (Ao) pressure remained unchanged during the procedure.

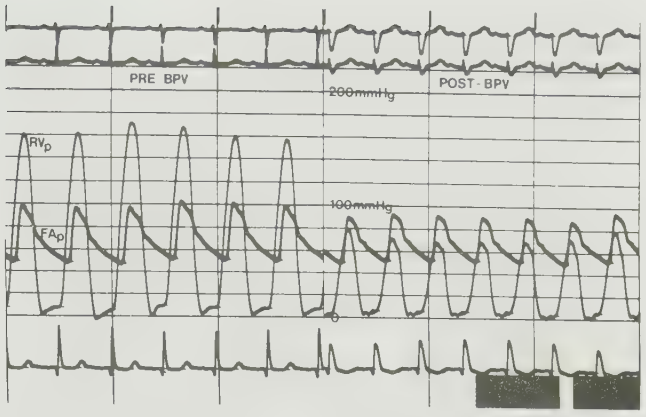

Fig. 81–18. Cardiac catheterization data obtained during balloon pulmonary valvuloplasty for severe stenosis in a five-month-old infant. Before valvuloplasty (PRE-BPV), the right ventricular systolic pressure (RVp) is approximately 170 mm Hg as compared to the femoral artery systolic pressure (FAp) of 100 mm Hg. After ballooning (POST-BPV), the RVp decreased to 70 mm Hg while the FAp diminished slightly to 95 mm Hg. The triangular RVp curve remained after balloon valvuloplasty and indicated some persistent obstruction. This infant had angiographic evidence of infundibular spasm that later resolved spontaneously. Note that the patient also had transient bundle branch block on the electrocardiogram.

nondysplastic pulmonic valve stenosis if the severity warrants intervention. Surgical valvotomy or valvectomy should be reserved for those patients in whom balloon valvuloplasty is unsuccessful or for those with dysplasia of the pulmonary valve.

Surgery

Sellors[251] and Brock[252] reported the first successful attempts at operative relief of pulmonary valve stenosis with intact ventricular septum. An initial experience of poor relief of obstruction from this technique led other surgeons to attempt valvotomy under hypothermia and direct visualization through the pulmonary artery.[253,254] Larger numbers of patients have now been treated by using cardiopulmonary bypass with transarterial pulmonary valvotomy.

Varco introduced the technique of inflow occlusion with "blind" pulmonary valvotomy in 1951.[255] Later, Mistrot and colleagues reported the successful use of inflow occlusion for isolated pulmonary valve stenosis in 110 patients ranging from two days to 36 years old.[256] Sade and associates demonstrated that inflow occlusion with transarterial valvotomy was as successful, as safe,

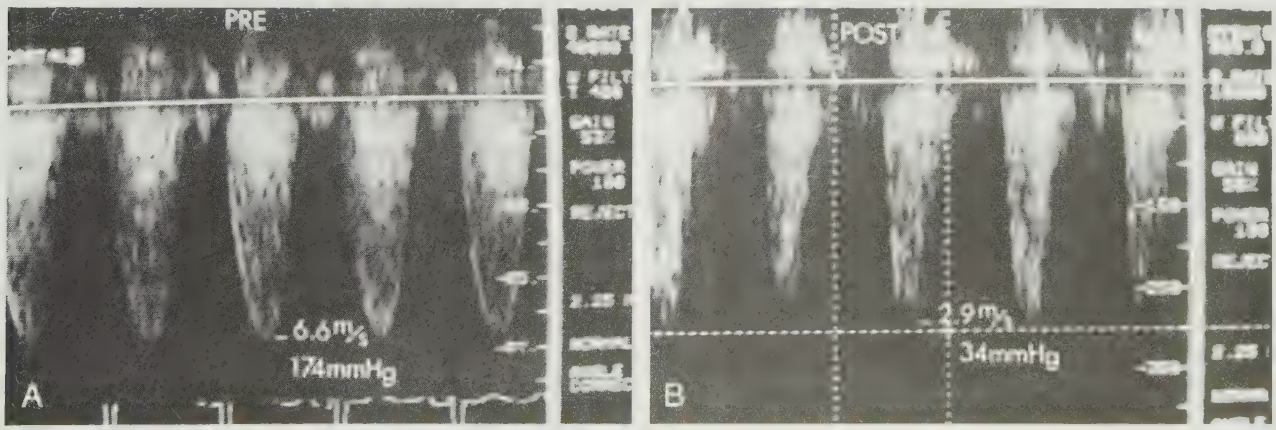

Fig. 81–19. Continuous-wave Doppler echocardiograms before (PRE) and after (POST) balloon valvuloplasty for severe pulmonary stenosis in the same infant mentioned in Figure 81–18. (A) The Doppler recording obtained from a subcostal approach before treatment demonstrated an instantaneous peak systolic transvalvular gradient of 174 mm Hg, using the modified Bernoulli equation: $PG = 4V^2$, where PG = pressure gradient and V = 6.6 m/s. (B) After balloon valvuloplasty has been completed, the peak systolic flow across the pulmonary valve decreased to 2.9 m/s. This would calculate to a postballooning transvalvular systolic gradient of approximately 34 mm Hg.

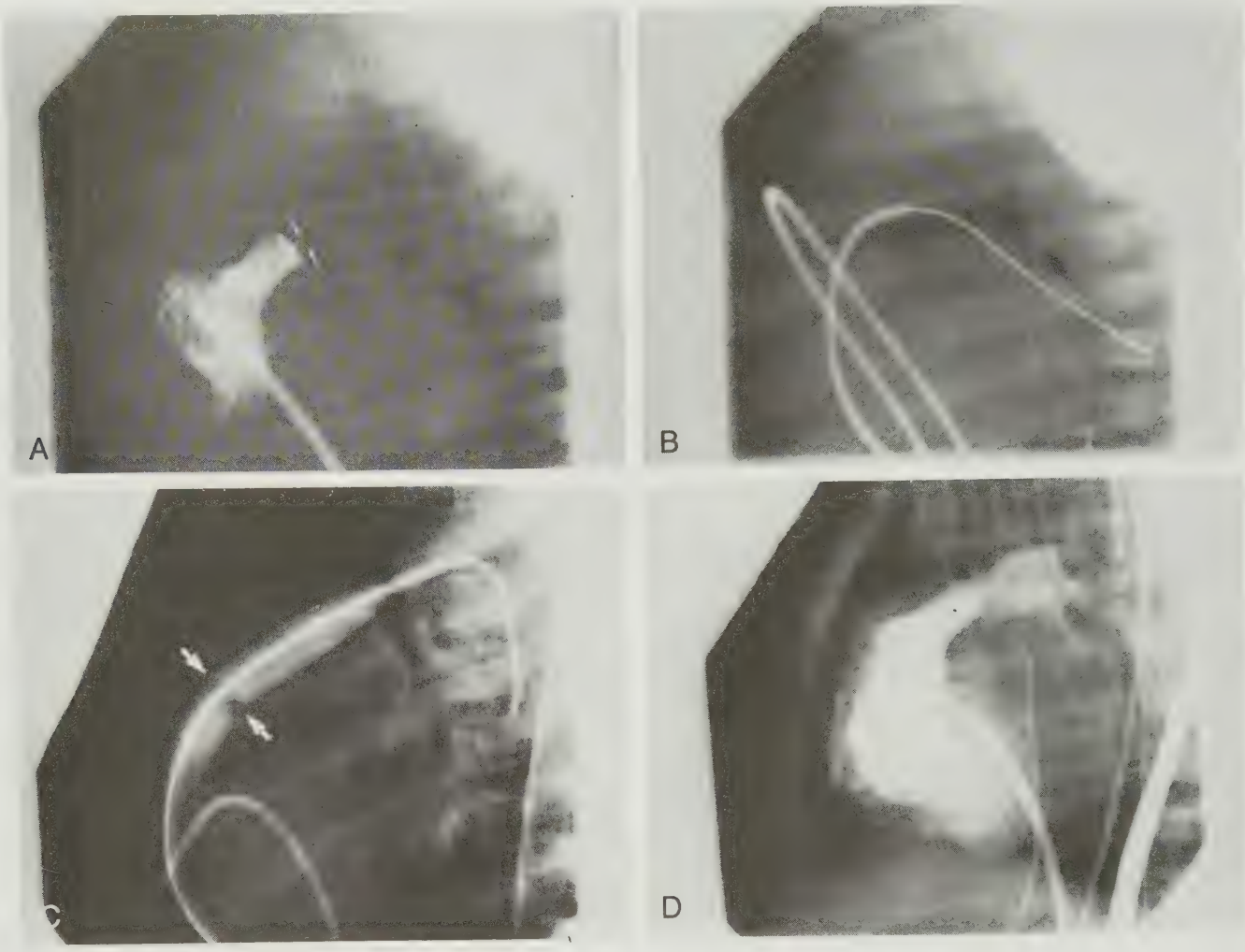

Fig. 81–20. Graduated sequential balloon valvuloplasty in a newborn with critical pulmonary valve stenosis and intact ventricular septum. (A) The lateral projection of a right ventriculogram demonstrates a tiny "jet" of prograde flow through the stenotic valve (arrows). The patient had a large patent ductus arteriosus supplying pulmonary blood flow, similar to pulmonary atresia with intact ventricular septum. (B) A guidewire was inserted across the stenotic pulmonary valve and placed into the distal pulmonary artery. An end-hole catheter was then advanced over the guide wire to dilate the pulmonary valve so that a balloon catheter could be passed through the tight orifice. (C) Next, a balloon catheter was placed across the stenotic pulmonary valve and inflated to outline the "waist" (arrows). After full inflation of the balloon, the waist disappeared. The presence of a patent ductus arteriosus is helpful to sustain pulmonary blood flow while obstructing right ventricular output during balloon inflation. (D) A repeat right ventriculogram revealed markedly improved prograde flow through the stenotic pulmonary valve.

and more cost effective than cardiopulmonary bypass for children with pulmonary stenosis.[257] However, in extremely ill infants, the closed or opened valvotomy using inflow occlusion is used as an emergency procedure. Lower mortality and morbidity with cardiopulmonary bypass for pulmonary stenosis surgery than in the past for young infants with critical pulmonary stenosis may be attributed to improved techniques for myocardial protection. These techniques are invaluable if a transannular patch or extensive infundibular resection is required in addition to pulmonary valvotomy or valvectomy.[258–261]

In rare instances, fatal right ventricular failure occurs ("suicide right ventricle") after an apparently successful valvotomy, presumably secondary to infundibular spasm.[262] It has been suggested that after adequate surgical pulmonary valvotomy, there is no need to explore and proceed with infundibular resection in patients with residual right ventricular pressure equal to systemic arterial pressure measured immediately after surgery.[263] In the same study, continuous postoperative right ventricular pressure monitoring demonstrated a 50% reduction in pressure over the first 24 hours. Propranolol may be given in an attempt to reduce infundibular narrowing and to differentiate dynamic from fixed subvalvular obstruction.[264]

When pulmonary stenosis is caused by a dysplastic valve, simple valvotomy is an inadequate surgical procedure. A partial or, more likely, a total pulmonary valvectomy is required.[265–267] In addition to removal of the thickened, immobile valve leaflets, insertion of a transannular patch is sometimes necessary because of the hypoplastic annulus and main pulmonary trunk. Patients who have undergone pulmonary valvectomy are left with at least a moderate degree of pulmonary insufficiency. Although a recent surgical study reports the long-term effectiveness and absence of symptoms at rest after five years in this patient population, there is still

concern regarding right ventricular function at rest and with exercise years after pulmonary valvectomy.[267]

The mortality from surgery is relatively low in both adults and children. In the Mayo Clinic series, the mortality rate was 4% in patients with pulmonary valve stenosis and intact ventricular septum.[268] Among 304 patients operated upon for pulmonary stenosis in the U.S. Joint Study, 9 died (3% mortality), and all of the deaths occurred in infants younger than one week of age. In the Toronto series, the surgical mortality in children younger than 12 years of age was 7%.[269] Bashour and colleagues also reported a surgical mortality of approximately 4%.[270] However, it is clear from the report of Coles and associates that the surgical risk for the neonate with critical pulmonary valve stenosis is quite high.[271] In this study, the overall hospital mortality is 42%, which was actually higher than the risk for pulmonary valve atresia with intact septum. The authors stressed the importance of establishing adequate extracardiac pulmonary blood flow in these critically ill neonates by infusion of prostaglandin E_1 or systemic-pulmonary shunt. Obviously, many of these infants had hypoplastic and/or poorly functioning right ventricles.

Postoperatively, the right ventricular pressure falls considerably. It is likely that 75% of patients with mildly elevated right ventricular pressures immediately after the operation will have a return to normal pressure after one to two years.[246] The U.S. Joint Study demonstrated that of 294 operated patients, only 10 had a right ventricular to pulmonary artery gradient of more than 50 mm Hg at recatheterization four to eight years after surgery.[76] Only one of these patients had transarterial valvotomy on cardiopulmonary bypass. At present, there is no strong evidence of restenosis. These data strengthen the argument for treatment intervention in children with resting transvalvular pulmonary gradients exceeding 50 mm Hg.

The incidence of postoperative pulmonary insufficiency varies from 57 to 90%.[76,245,272] Although this does not create immediate problems in most instances, the possibility of deleterious effects in later years from chronic diastolic overload of the right ventricle is certainly possible. A recent study demonstrated improved right ventricular function following late pulmonary valve replacement for residual pulmonary insufficiency after tetralogy of Fallot repair.[273] This issue is very controversial for the population of patients with tetralogy of Fallot surgery, and data from that population may not reflect the situation for patients with pulmonary stenosis. There are very few reports of late complications after pulmonary valve surgery. Late arrhythmias appear to be rare. We could find no cases of late sudden death in this patient population. Wright and Moller reported residual right-to-left atrial shunting following pulmonary valvotomy without closure of an atrial communication.[274] Exercise abnormalities were mentioned earlier in the chapter and appear to be more common in adults who had late repair.[147] In McNamara and Latson's study, 3 of 13 postoperative patients undergoing treadmill exercise testing demonstrated premature ventricular beats.[272]

Recreational, Occupational, and Insurability Recommendations

The pediatric cardiologist is often asked the extent to which physical activity should be restricted in the child with pulmonary valve stenosis, either treated or untreated. In 1986, a special report was issued by an American Heart Association committee representing the Council on Cardiovascular Disease in the Young stating the recreational and occupational recommendations for young patients with heart disease.[275] The committee recommended *no restriction* of physical activities, allowing endurance training, interscholastic athletics, and contact sports in all patients with operated or unoperated mild pulmonary valve stenosis. In patients with mild obstruction, occupational activity may include *very heavy work* to include a peak load of 7.6 cal/min and above, lifting of objects in excess of 100 lb, and frequent lifting and/or carrying of objects weighing 50 lb or more.

In patients with operated or unoperated moderate pulmonary valve stenosis, *light exercise* was recommended. This is to include nonstrenuous team games, recreational swimming, jogging, cycling, and golf. Allowable occupational activity is classified as *medium work*. This classification includes a peak load of 5.0 to 7.5 cal/min, lifting a maximum of 50 lb and frequent lifting and/or carrying of objects weighing up to 25 lb.

As expected, children with severe pulmonary valve stenosis with or without intervention have more restriction of activities. A recreational classification of *moderate limitation* is advised which includes attending school but no participation in physical education classes. The occupational activity category of *light work* is recommended in this group of patients. This includes a peak load of 2.6 to 4.9 cal/min, lifting 20 lb maximum, and frequent lifting and/or carrying of objects weighing up to 10 lb. Jobs that require considerable walking or standing or those that require mostly sitting with some pushing and pulling of arm and/or leg controls are acceptable.

A special task force issued recommendations regarding eligibility for competition in athletes with congenital heart disease.[276] Recommendations were as follows:

1) Patients with an unoperated peak systolic pulmonary transvalvular gradient of less than 50 mm Hg and normal right ventricular function may participate in all competitive sports.
2) Patients with an unoperated peak systolic pulmonary valve gradient of 50 mm Hg or more and/or evidence of right ventricular dysfunction can participate in low-intensity sports, including bowling, cricket, curling, golf, and riflery. Patients in this category are usually referred for balloon pulmonary valvuloplasty or alternatively for surgical valvotomy.
3) Patients with adequate operative relief of obstruction (mild pulmonary valve stenosis) and normal right ventricular function six months after surgery can participate in all competitive sports. If balloon valvuloplasty is performed, a shorter interval after relief of the gradient may apply.
4) Patients with persistent moderate-to-severe pulmonary valve stenosis after surgery should follow the same recommendations as for preoperative patients. The committee also stated that the minimal diagnostic evaluation required before a decision is made regarding participation in athletics in a patient whose electrocardiogram and physical examination suggest moderate or severe pulmonary stenosis includes measurement of gradient by cardiac catheterization and evaluation of right ventricular function by angiography, two-dimensional echocardiography, or nuclear medicine–quantitated ventricular ejection fraction. The use of

continuous-wave Doppler echocardiography may accurately predict the transvalvular gradient.

Another problem that commonly faces the patient with congenital heart disease is the ability to qualify for health and life insurance. In 1980, the Committee on Insurability of the Council on Cardiovascular Disease in the Young and representatives of the Association of Life Insurance Medical Directors of America jointly developed guidelines.[277] Children with trivial pulmonary valve stenosis (systolic gradient less than 15 mm Hg) are insurable at a standard rating. Patients with mild pulmonary valve stenosis (systolic gradient between 15 and 45 mm Hg) have standard-to-minimum substandard insurable rating. Moderate pulmonary valve stenosis (transvalvular gradient between 46 and 79 mm Hg or a right ventricular systolic pressure of 50 to 74% of systemic systolic pressure) requires a moderate-to-heavy substandard rating of insurability. Children with severe pulmonary valve stenosis (peak systolic gradient greater than 79 mm Hg or right ventricular systolic pressure greater than 74% of systemic systolic pressure) are probably uninsurable.

When assessing the patient's postoperative hemodynamics, the committee divided the group into those with excellent surgical results and those with less than excellent results. The criteria for excellent results are 1) lack of symptoms, 2) absence of cyanosis, 3) normal chest film except dilated main pulmonary trunk, 4) normal electrocardiogram or mild right ventricular hypertrophy, and 5) a peak systolic transvalvular gradient less than 25 mm Hg if catheterized. Patients who fulfill the above criteria for excellent surgical results should have a standard rating for insurability. The criteria for less than excellent surgical results are similar to the preoperative criteria for mild, moderate, and severe stenosis. Trivial-to-moderate pulmonary insufficiency does not alter postoperative classification. Patients with less than excellent surgical results are insurable at a rating that corresponds to the residual hemodynamics as classified by the preoperative state.

INTRACAVITARY OBSTRUCTION OF THE RIGHT VENTRICLE

The next portion of the chapter briefly discusses the various forms of intracavitary obstruction of the right ventricle. The two types of obstruction may be classified as primary infundibular stenosis and double-chambered right ventricle secondary to an anomalous muscle bundle.

Pulmonary Infundibular Stenosis

Background, Prevalence, Pathology, and Embryology

Primary infundibular stenosis with intact ventricular septum is a very uncommon defect; it was initially described by Elliotson in 1830.[278] This rare entity accounts for only approximately 5% of all cases of right ventricular outflow tract obstruction. Primary infundibular stenosis has been separated into two types:

1) A fibrous band at the junction of the infundibulum and main body of the right ventricle. This is the more common type and closely resembles the double-chambered right ventricle.
2) Fibromuscular obstruction directly beneath the pulmonary valve.

The proposed embryologic abnormality for both types is an arrest of bulbus cordis involution that, along with the ventricular sinus, forms the outflow tract.[25]

Pathophysiology and Manifestations

The pathophysiology of primary infundibular stenosis is similar to that already described for pulmonary valve stenosis. The clinical manifestations of these two disorders are indistinguishable from each other. The signs and symptoms depend upon the severity of obstruction and the association of other cardiac defects. The physical findings consist of a loud, systolic ejection murmur that may be accompanied by a thrill. The first sound is normal with a widely split second sound and soft pulmonary component.

Two findings that help to distinguish infundibular from pulmonary valvar stenosis are the lower precordial location of the murmur and the absence of an ejection click in infundibular stenosis. However, it is often very difficult to differentiate the two disorders clinically. The electrocardiographic features of infundibular stenosis are similar to those of pulmonary valve stenosis. Levine and Blumenthal suggested that the infundibular stenosis is more likely to progress in severity, as noted on the electrocardiogram, than is pulmonary valve stenosis.[190] With the exception of a dilated pulmonary trunk, the radiographic features of infundibular and pulmonary valvar stenosis are similar. Weyman first demonstrated the ability to differentiate obstruction at the infundibular area from that at the valve site using M-mode echocardiography.[100] The pulmonary valve usually demonstrates systolic fluttering secondary to the valve being moved by the turbulent flow from the infundibular obstruction. The A dip may be absent in severe cases. Two-dimensional, Doppler, and color flow echocardiography help considerably in distinguishing infundibular from valvar stenosis. When the infundibular stenosis is directly beneath the valve, the distinction may be difficult. However, when systolic fluttering of the valve is noted rather than doming, the diagnosis of subvalvular obstruction is much more likely. We have found the parasternal right ventricular outflow view and the subcostal inflow–apex–outflow view of the right ventricle to be very helpful. It is also possible to estimate the severity of obstruction by using continuous-wave Doppler echocardiography, but care must be taken to align the transducer parallel to the turbulent flow.

Cardiac Catheterization

During cardiac catheterization, the pullback pressure recording should be obtained by using an end-hole catheter. If the obstruction is at the junction of the main right ventricular body and infundibulum, then the pressure obtained in the subvalvular area will be equal to the pulmonary artery pressure with a higher right ventricular pressure in the main cavity. In contrast, when the stenosis is immediately beneath the pulmonary valve, the pullback pressure recording may be indistinguishable from pulmonary valve stenosis. A selective right ventriculogram with the anteroposterior camera in the standard position or with 40° cranial angulation and a straight lateral projection demonstrates the site of infundibular obstruction quite nicely. The narrowing is usually constricted during systole, with a normal pulmonary valve, and no poststenotic dilatation of the main pulmonary artery is noted.

Differential Diagnosis

The list of differential diagnoses is long and very similar to that for pulmonary valve stenosis. The murmur most likely to be confused with infundibular stenosis is from a ventricular septal defect. The lower location of the infundibular stenosis murmur and absence of an ejection click makes it difficult to differentiate this

diagnosis from ventricular septal defect. Characteristics of the murmur that would favor the diagnosis of infundibular stenosis are ejection systolic murmur, radiation to pulmonary arteries, and a widely split second sound with a soft pulmonary component. If the murmur is holosystolic with a left ventricular lift and diastolic flow rumble over the mitral valve, then the diagnosis of ventricular septal defect is likely. The electrocardiogram and chest roentgenogram may be helpful in distinguishing between these two defects. Echocardiography is frequently necessary to make the distinction among infundibular obstruction, pulmonary valve stenosis, and ventricular septal defect.

Treatment

Although infundibular stenosis has reportedly been treated with balloon dilation, there is a significant risk of valve avulsion and intramyocardial hemorrhage, thus limiting the applicability of dilation techniques at this time.[213] Therefore the treatment of choice in significant primary infundibular stenosis is surgical resection of the fibrotic area or hypertrophic muscle.[38,279,280] It is occasionally necessary to use a right ventricular outflow tract patch with some forms of infundibular stenosis. Because progression of severity in obstruction may be more rapid with this disease, closer followup may be warranted. Appropriate antibiotic prophylaxis is necessary for both operated and untreated primary infundibular stenosis with intact ventricular septum.

Double-Chambered Right Ventricle

Background, Prevalence, Pathology, and Embryology

Since Lucas described the first cases of double-chambered right ventricle in 1962 as a new entity to be separated from other forms of right ventricular outflow tract obstruction, more than 100 cases have been reported.[281–287] The obstruction is caused by anomalous bands of muscle oriented so as to divide the right ventricular cavity into a proximal high-pressure chamber and a distal low-pressure chamber.[288–293] The anomalous muscle bundles are hypertrophic, constituting a pyramid-shaped mass running between the ventricular septum inferior to the insertion site of the tricuspid valve septal leaflet to the right ventricular anterior free wall. There are commonly two bundles, the ventral and the dorsal. The ventral bundle is smaller, is more superficial, and attaches to the right ventricular wall adjacent to the septum. The dorsal bundle is larger and thicker and has its attachment at the anterior papillary muscle base.[35]

In contrast to tetralogy of Fallot, the anomalous muscle bundles cross the right ventricular cavity and lie proximal to the infundibulum. They frequently occur at the sinus portion of the right ventricle or along the distal or apical portion of the inflow. Although the moderator band is a normal structure that may be confused with anomalous muscle bands, there are some noteworthy differences. The orientation of the anomalous bands are different from that of the moderator band. The anomalous muscle bundles have their septal attachments more basally near the tricuspid valve annulus, while the insertion site of the moderator band is in the apical third of the ventricular septum. Both types of bands attach to the right ventricular free wall, but the unobstructive moderator band lies toward the septal side of the cavity, while the obstructive anomalous bands cross the main cavity.

There has been speculation regarding the etiology of these anomalous muscle bundles. Keith suggested that the embryologic explanation for this malformation is an arrest of the incorporation of the primitive bulbus cordis into the body of the right ventricle.[25] An improper expansion of the bulboventricular junction may result in the incomplete fusion of the bulbar and endocardial cushions that are responsible for closing the superior ventricular septum. This theory would explain the common occurrence of an associated ventricular septal defect, which is observed in up to 93% of cases.[287] Some investigators think that isolated forms of double-chambered right ventricle do not exist, but rather a previously patent ventricular septal defect closed spontaneously.[284,294] Others attributed this anomaly to persistence of early myocardial cells or trabeculations.[281,286] It has also been postulated that the obstruction in the double-chambered right ventricle is caused by an elevated origin of a hypertrophied moderator band from the septal band.[284] In most severe forms, this band originates near the crista supraventricularis, resulting in an unusual and different orientation from that of the normal moderator band. Rowland and co-workers view this muscular tissue as "anomalous" only in representing arrest in development of the right ventricle.[284] Other groups support the hypothesis of inadequate bulbar incorporation because of the association of discrete subaortic stenosis with this lesion, as well as with ventricular septal defect.[284,294,295] Bashour and co-workers reported double-chambered right ventricle with a fibromuscular diaphragm similar to that found in subaortic stenosis.[296]

Pathophysiology and Manifestations

The pathophysiology of this disease is similar to that of the other forms of intracavitary obstruction of the right ventricle with intact ventricular septum. The obstruction is between the inflow and outflow portions of the ventricle, and there may be a further compromise in the diameter of this area during ventricular systole. A nonobstructive anomalous muscle bundle in infancy may become obstructive with time.[284,286,289] Clinically, patients with double-chambered right ventricle are similar to those with pulmonary valvar or infundibular stenosis. Since ventricular septal defect is so commonly present, this may influence the clinical manifestations. A prominent diamond-shaped systolic murmur with thrill is frequently heard along the left lower sternal border. It may be indistinguishable from the murmur of infundibular stenosis. A significant left-to-right shunt from the ventricular septal defect should be suspected if a mid-diastolic flow rumble is present over the mitral valve area. Typically, a click is absent, and the pulmonary component of the second sound is normal.

The chest roentgenogram is similar to that of infundibular stenosis unless a significant ventricular septal defect is also present. In most patients, the electrocardiographic patterns are those of right ventricular hypertrophy. A recent study by Li and colleagues demonstrated the presence of an upright T wave in lead V_3R as the only finding suggestive of right ventricular hypertrophy in as many as 40% of patients with double-chambered right ventricle.[291] In milder cases of obstruction, a normal electrocardiogram was seen initially, but there was progression to right ventricular hypertrophy as the muscular obstruction increased.[289] However, normal electrocardiograms have been reported in patients with severe obstruction.[297] Folger reported a reproducible electrocardiographic appearance with double-chambered right ventricle to be a right superior vector orientation and rightward displacement of the electrocardiographic right ventricular hypertrophy pattern.[298] He later

ascribed this abnormality to a right ventricular pouch noted on angiography.[299]

Echocardiography may be very helpful in diagnosing double-chambered right ventricle. Initially, Fermont and colleagues stated that the diagnosis of this disorder was suggested by the presence of the following M-mode features: easy visualization of the pulmonary valve, premature closure and systolic fluttering of the pulmonary valve, and false septoaortic discontinuity.[300] Two-dimensional echocardiography has improved diagnostic accuracy in this lesion.[287,297,301,302] Direct imaging of the anomalous muscle bundle using the subcostal inflow–apex–outflow view and the subcostal short-axis view has improved diagnostic capabilities and allowed better understanding of the unusual intracardiac anatomy (Fig. 81–21).

Cardiac Catheterization

Cardiac catheterization is frequently necessary for more definitive assessment. The systolic pressure in the distal portion of the double-chambered right ventricle is usually normal and equal to the pulmonary artery systolic pressure. The gradient across the anomalous muscle bundle is detected by placing the catheter into the proximal inflow portion of the right ventricle and then advancing to the distal outflow chamber. Since it is technically quite easy to place the catheter from the right atrium directly into the right ventricular outflow tract, the pediatric cardiologist must be aware of potentially "missing" the high-pressure inflow portion of the ventricle. Therefore we advise placing the catheter into the right ventricular inflow and apical region in all patients undergoing cardiac catheterization for ventricular septal defect. Selective right ventriculography is imperative for diagnosis and may be performed in the standard anteroposterior and lateral projections or with cranial angulation of the anteroposterior camera.[303–305] We prefer to perform the injection with the catheter in the high-pressure portion of the double-chambered right ventricle for better anatomic detail of the anomalous muscle bundle (Figs. 81–22 and 81–23A, B). However, Folger described a contractile, right ventricular outflow pouch in approximately 60% of patients that was best demonstrated with the low-pressure distal chamber as the injection site.[299] Although the filling defect secondary to the anomalous muscle band is constant throughout the cardiac cycle, it is best appreciated during ventricular systole. A left ventricular angiogram with left anterior oblique and cranial angulation is important to rule out an associated ventricular septal defect or subaortic valve membrane. Since Danilowicz and Ishmael reported an extraordinarily high incidence of renal anomalies in patients with anomalous right ventricular muscle bundle (43%), we recommend close inspection of the kidneys, ureters, and bladder after cineangiography has been completed.[297]

Treatment

The treatment of double-chambered right ventricle with significant obstruction is surgery.[291–293] We do not recommend attempting balloon dilation of these obstructions. Warden and associates noted at the time of surgery that during ventricular contraction, a "dimple" on the usually smooth right ventricular surface suggested the presence of an anomalous muscle bundle.[293] The "dimple" corresponds to the parietal attachment of the ventral limb of the muscle band and is located midway between the base and apex near the anterior interventricular groove. A right ventriculotomy is necessary, and transection of the parietal and septal origin sites must be performed first. It is extremely important to have complete exposure of the anterior papillary muscle and tricuspid valve to avoid injury during the resection of the insertion sites of the anomalous muscle band.[293] The associated ventricular septal defect is also closed at the time of operation.

Although the long-term prognosis for these patients is unknown,

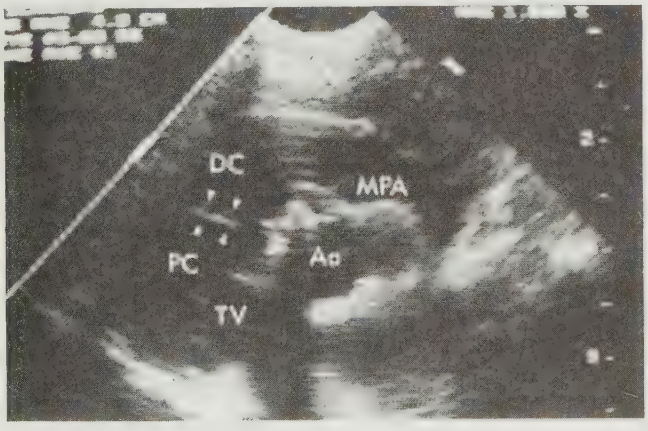

Fig. 81–21. A two-dimensional echocardiogram in a patient who developed double-chambered right ventricle after surgical closure of a ventricular septal defect. We used a modified subcostal inflow–apex–outflow view. The tricuspid valve (TV) leaflets are seen leading into the proximal chamber (PC) of the right ventricle. This chamber is the high-pressure portion of the ventricle. The anomalous muscle bundle (arrows) is seen dividing the right ventricle into a proximal and a distal chamber (DC). This low-pressure outflow chamber empties through the pulmonary valve into the main pulmonary artery (MPA). A bright echo representing the ventricular septal defect patch is seen near the aorta (Ao) at approximately 9 to 11 o'clock.

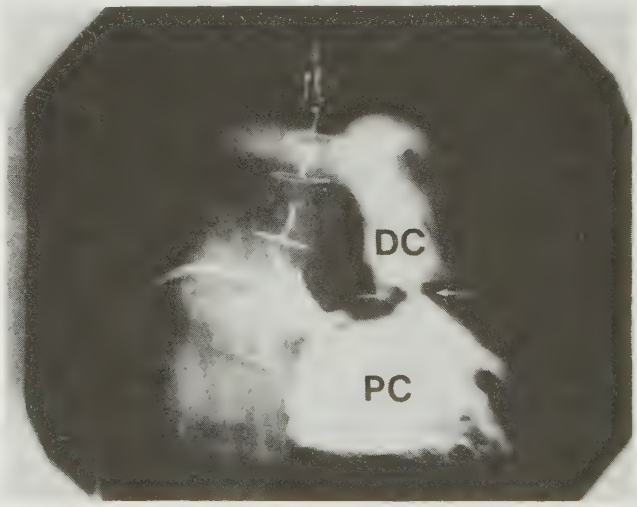

Fig. 81–22. A right ventriculogram in a child with double-chambered right ventricle after closure of a ventricular septal defect in the same patient as in Figure 81–21. A large fibromuscular ridge (arrows) is shown dividing the right ventricle into a high-pressure proximal chamber (PC) and a low-pressure distal chamber (DC). The pulmonary valve is seen widely open in systole without dilatation of the main pulmonary artery.

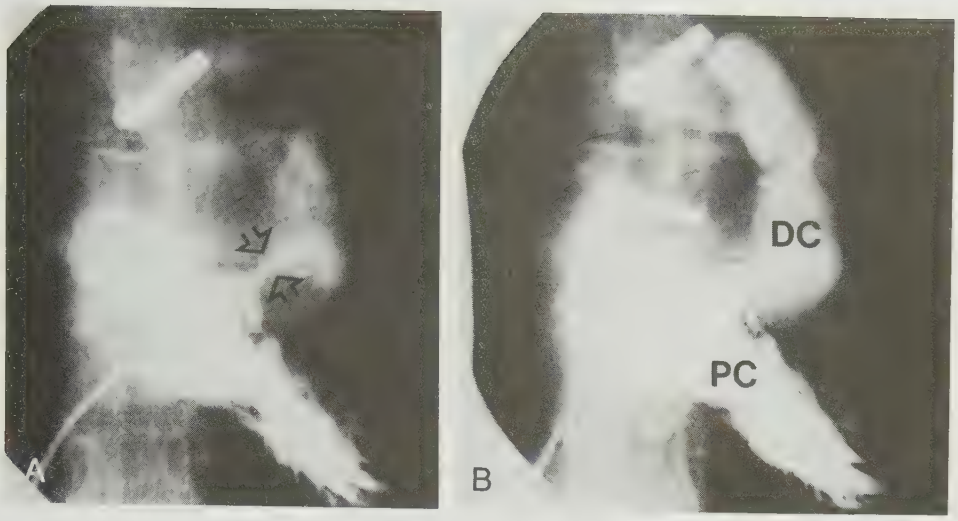

Fig. 81–23. A right ventriculogram in a teenager with a double-chambered right ventricle who had a ventricular septal defect repaired in early childhood. (A). The initial injection is into the proximal chamber with a discrete "jet" of contrast material streaming into the distal chamber as depicted by the arrows. (B). After several more cineangiograph frames, both the proximal and distal chambers (PC, DC) are well seen. It is easy to understand how the term "double-chambered right ventricle" came into existence after seeing this angiocardiogram.

the short-term surgical results appear good. In the untreated condition, double-chambered right ventricle secondary to an anomalous muscle bundle appears to be a progressive disease. Patients with this disorder should be followed as outpatients every six months as infants and young children and yearly as older children. The electrocardiogram and echocardiogram should prove useful in detecting changes in the severity of obstruction and selecting patients for cardiac catheterization and surgery. Appropriate antibiotic prophylaxis for infective endocarditis is indicated.

PULMONARY ARTERY STENOSIS

Background

Obstruction in the pulmonary arterial tree distal to the pulmonary valve has been described by using various terms: partial atresia or hypoplasia of the pulmonary arteries, supravalvular pulmonary stenoses, coarctation of the pulmonary arteries, and postvalvular, multiple, or peripheral pulmonary stenoses. A number of classifications have been made, but those of Smith[306] and Franch and Gay[307] are the most widely used. They identify the area of the pulmonary artery most severely affected, such as the proximal main pulmonary artery, bifurcation of the main pulmonary artery, distal pulmonary arteries, or various combinations. Rowe described another classification based upon simple or complicated cardiac malformations as well as the site of obstruction.[308] Simple pulmonary artery stenoses were classified as isolated or pulmonary artery obstruction associated with simple cardiac diseases. Complex pulmonary artery stenoses usually have tetralogy of Fallot or transposition of the great arteries associated with the obstruction. Both simple and complex stenoses are further separated into sites of obstruction: central, peripheral, or intermediate. The stenoses may be unilateral or bilateral.

Prevalence

The overall frequency of pulmonary arterial stenosis is an estimated 2 to 3% of congenital heart disease.[309,310] Isolated pulmonary arterial stenosis was initially reported by Mangars in 1802 and later by Schwalbe.[311] There have been numerous reports of cases since this early report.[312–323] In one third of cases, the pulmonary artery stenosis is an isolated defect, but two thirds of patients have associated cardiac defects. The most frequent associated defects are pulmonary valve stenosis and ventricular septal defect.[9,324] Tetralogy of Fallot is also commonly seen with hypoplasia of the pulmonary branches.[9,320] If rubella syndrome is present, patent ductus arteriosus and atrial septal defect are also usually present.[316,325,326] A syndrome (Williams) with supravalvular aortic stenosis, multiple pulmonary arterial stenoses, elfin facies, and mental retardation has been described.[161,162,327] Other syndromes in which pulmonary artery stenoses are present include Noonan's, Alagille (arteriohepatic dysplasia), Ehlers-Danlos, cutis laxa, and Silver's syndromes.[29,308,318,322,328]

Embryology and Pathology

The pathogenesis of pulmonary artery stenosis is unknown, although multiple factors and many types of pathologic changes may produce vessel narrowing. A teratogenic agent may interrupt the development of any segment of the pulmonary arterial tree; for example, rubella virus may interfere with normal formation of elastic layers of the tissue.[329] The stenoses may be caused by a ring-like membrane, fibrous intimal and medial thickening, or abnormality of elastic tissue properties. In general, two thirds of patients demonstrate stenosis of the main pulmonary trunk, its bifurcation, or its main branches. Distal vessel dilatation occurs if the stenosis is localized, while only minimal poststenotic dilatation is present if an elongated constriction is present. Prestenotic dilatation of the main pulmonary trunk is very uncommon.

Pathophysiology

The pathophysiologic process of pulmonary artery stenosis results in elevation of the right ventricular and pulmonary arterial pressure proximal to the obstruction. If the stenosis is central, the right ventricular stroke volume cannot be increased readily secondary to the limited proximal pulmonary trunk volume capacity. With severe stenosis, the ejection time of the right ventricle is prolonged, a feature that explains the delayed pulmonic component of the second sound. If there is no associated pulmonary valve stenosis, the length and magnitude of vessel narrowing determine the contractile mechanics of the right ventricle. Orell and coworkers noted that closure of the pulmonary valve may occur

earlier than, and sometimes at the same time as, closure of the aortic valve if there are severe multiple peripheral stenoses of small pulmonary arterial branches.[330] In the absence of increased pulmonary flow, the right ventricular pressure is normal in unilateral pulmonary artery stenosis. The contralateral pulmonary circulation is able to accommodate the cardiac output without increase in pressure. It is uncertain, under conditions of normal pulmonary flow, whether the absolute pressure difference between the main trunk and the distal pulmonary artery is proportional to the severity of obstruction. However, it is known that the diastolic pressure difference between the main trunk and the pulmonary artery branch is directly proportional to the severity of obstruction.

Manifestations

The clinical features of pulmonary artery stenosis may easily be masked by the other associated cardiac defects. However, close inspection and auscultation reveal a systolic ejection murmur heard over the pulmonary area but better transmitted to the back and lateral lung fields. A click is usually absent unless pulmonary valve stenosis is also present. A continuous murmur may be present in up to 10% of patients and indicates that the diastolic gradient across the obstruction is significant.[315] Though the murmur varies according to severity, it usually peaks in late systole. The first sound is normal, while the second sound is usually normal in intensity and width of splitting. In patients with significant multiple peripheral pulmonary arterial stenoses, the second sound in the pulmonary artery may be quite loud and confused with pulmonary hypertension. In these patients, the presence of continuous murmurs in the back and axilla should lead one to the correct diagnosis.

A transient murmur resembling that of pulmonary arterial stenosis is frequently heard in healthy, premature infants during the first few months of life and is considered "physiologic."[331] This murmur has also been reported in young full-term infants as well. It is believed to be secondary to the disparity of main pulmonary trunk size, diameter of pulmonary branches, and the acute angle between the trunk and the branches.[332]

Patients with mild-to-moderate arterial obstruction are asymptomatic, while those with severe stenosis may have dyspnea on exertion, easy fatigability, and occasionally right-sided heart failure. Cyanosis may occur if there is an intracardiac or extracardiac right-to-left shunt. Progression from relatively mild to severe symptomatology occurred in two reported fatal cases in less than two to four years.[323,330]

Electrocardiogram, Roentgenogram, and Echocardiogram

The electrocardiogram in mild cases is usually normal. Varying degrees of right ventricular hypertrophy are present in patients with moderate-to-severe pulmonary artery stenosis and are indistinguishable from those of pulmonary valve stenosis (Fig. 81–24). In a group of infants with rubella syndrome, a high frequency of left-axis deviation was noted.[333] A similar electrocardiogram was reported in infants with Noonan's syndrome.

The radiographic features of pulmonary artery stenosis are unremarkable. The chest roentgenogram is normal unless there are other significant associated cardiac defects (Fig. 81–25).

The echocardiogram may be helpful in the diagnosis of pulmonary arterial stenosis and other associated cardiac defects. However, there are several caveats. The more distal pulmonary artery branches cannot be adequately imaged for diagnostic purposes. As Tinker and associates reported, we have also found the parasternal short-axis and suprasternal/supraclavicular short-axis views to be the most helpful in imaging the main pulmonary trunk and right and left branches.[334] Doppler echocardiographic estimation of gradient across the stenosis is extremely difficult and frequently inaccurate. Color flow mapping may improve the accuracy of qualitative assessment. If there is evidence of a significant systolic gradient, right ventricular hypertension and hypertrophy, or significant tricuspid, and/or pulmonary insufficiency, then cardiac catheterization is recommended.

It is possible that computerized tomography, magnetic resonance imaging, and dynamic spatial reconstruction may be useful in the anatomic evaluation of pulmonary arterial stenosis. A recent report utilized chest computerized tomography to diagnose a bronchogenic cyst causing external compression of the pulmonary artery.[335] We have recently utilized nuclear medicine lung perfusion/ventilation scans in patients being considered for interventional therapy (Fig. 81–26). This test has helped to "quantitate" changes

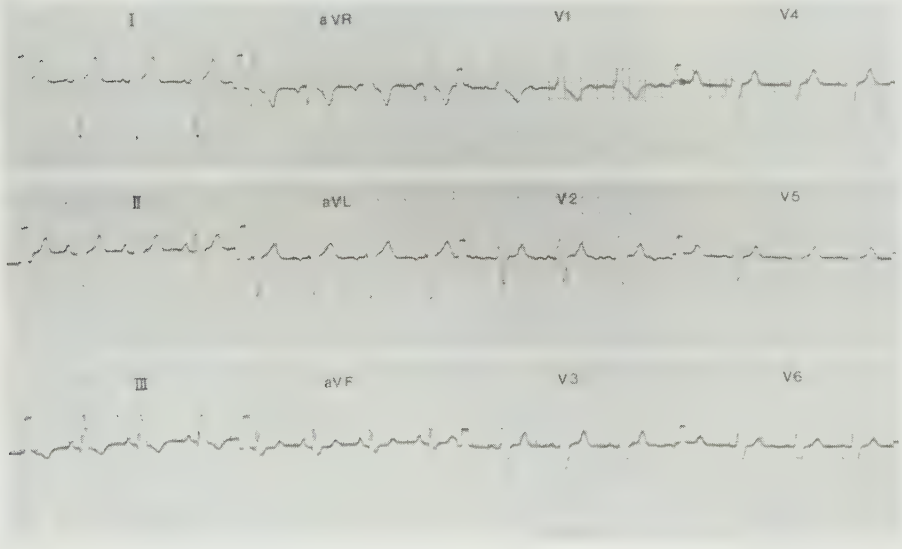

Fig. 81–24. An electrocardiogram in an adolescent boy with severe peripheral pulmonary artery stenosis secondary to Williams syndrome. Note that the precordial leads V_1 to V_6 are half-standard. Right bundle branch block versus severe right ventricular hypertrophy is observed.

Fig. 81–25. The chest film in a patient with severe peripheral pulmonary artery stenoses is quite unremarkable. The heart size is normal, and the pulmonary vascular markings are within the range of normal. The chest roentgenogram does not reflect the severity of pulmonary artery stenosis.

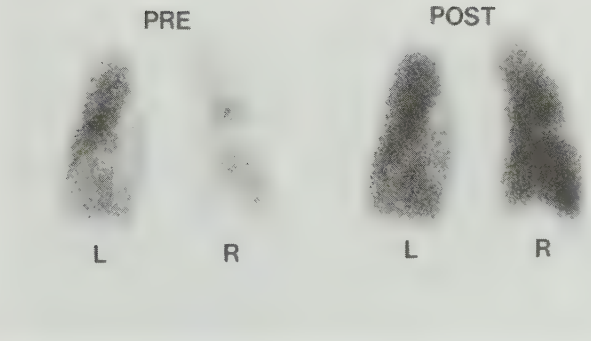

Fig. 81–26. A nuclear medicine perfusion scan in a patient undergoing balloon pulmonary angioplasty for right pulmonary branch stenosis. The views are from the posterior with the right lung (R) and left lung (L) labeled. Before angioplasty (PRE), there was differential perfusion of the lungs: 63% to the left, 37% to the right. After balloon dilation of the stenotic right pulmonary artery (POST), the perfusion to the right lung significantly increased to 52%, while the left lung perfusion was 58%. The use of perfusion/ventilation scans may help to quantitate the effects of balloon pulmonary arterioplasty.

in pulmonary blood flow, both globally and segmentally, before and after balloon pulmonary angioplasty.

Cardiac Catheterization

Cardiac catheterization is usually required for precise physiologic and anatomic diagnosis of pulmonary arterial stenosis. Particular attention needs to be paid during slow, pullback pressure recordings from the distal pulmonary arteries to the right ventricle using an end-hole catheter. In the absence of increased pulmonary blood flow, systolic pressure gradients greater than 10 mm Hg should be considered abnormal. Exceptions to this rule are in premature and young infants with a discrepant size in pulmonary branches and main pulmonary trunk or when the catheter is relatively large in comparison to the vessel diameter.[322] With isolated, unilateral stenosis, the pressure gradient is found at the site of obstruction with a normal pressure in the proximal pulmonary artery segment.

A peculiar appearance of the main pulmonary artery pressure pulse in patients with bilateral stenoses has been shown by Agustsson and colleagues.[312] The systolic portion of the main pulmonary artery pulse is identical to that of the right ventricle. However, while the diastolic pressure is normal, the dicrotic notch is abnormally deep with a flattened diastolic descent after pulmonary valve closure that appears to be proportional to the severity of distal obstruction. Rowe suggested that the diagnosis of bilateral pulmonary arterial stenosis should be suspected by the appearance of the main pulmonary artery pressure pulse alone.[308] Agustsson and colleagues attributed this characteristic pulse contour proximal to the stenosis to altered function of the pulmonary trunk.[312] A relatively nonelastic pulmonary trunk with thick, fibrotic walls becomes an extension of the right ventricular outflow tract. As long as the pulmonary artery pressure distal to the narrowing is less than the right ventricular pressure, the pulmonary valve remains open. As the obstruction sites are more peripherally located, this peculiar pressure pulse in the main pulmonary trunk becomes less obvious. When the stenoses are severe and more peripherally located, the proximal pressure pulse contour is indistinguishable from that of primary pulmonary hypertension. It is important to remember that the presence of associated pulmonary valve stenosis may negate the use of the main pulmonary trunk pressure pulse as a predictor of severity of peripheral stenoses.

Angiocardiography is the single best tool in delineating pulmonary arterial stenosis (Figs. 81–27A, B and 81–28A, B). Although a right ventriculogram is frequently performed, selective pulmonary arterial injections proximal to the site of obstruction are imperative. In most instances, 40° cranial angulation with or without appropriate obliquity is necessary in the anteroposterior projection with a straight lateral view.[336] Angiography has made it possible to classify the various types of obstruction.[307] It has also allowed the diagnosis of pulmonary arterial stenoses in complicated congenital heart disease to be made, even when it was not suspected from other studies. One should consider performing left ventricular or aortic angiography in these patients because of the possibility of associated systemic arterial lesions.

Differential Diagnosis

The differential diagnoses for pulmonary arterial stenosis are similar to those already mentioned for pulmonary valve obstruction. The characteristic radiation of the systolic ejection murmur

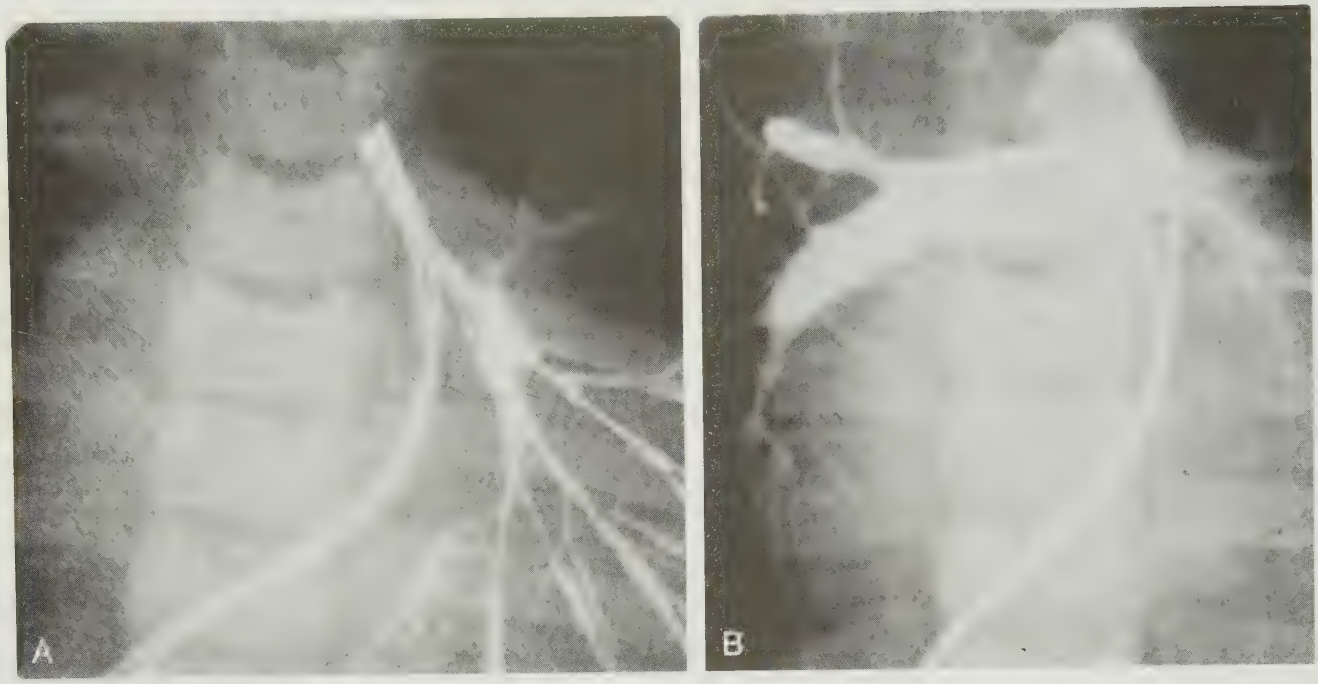

Fig. 81–27. Selective pulmonary angiograms in a child with severe peripheral pulmonary artery stenoses. (A). A left pulmonary arteriogram demonstrates severe, diffuse stenoses of all segments of the distal pulmonary arterial tree. Note the long hypoplastic segments and widespread severity. (B). The right pulmonary arteriogram also confirms complete distal involvement of the entire segmental arteries. Unfortunately, the results of balloon pulmonary angioplasty were unrewarding, and the patient continued to exhibit suprasystemic right ventricular pressure with cyanosis and right-sided congestive failure. No etiology has been found for this severe disease.

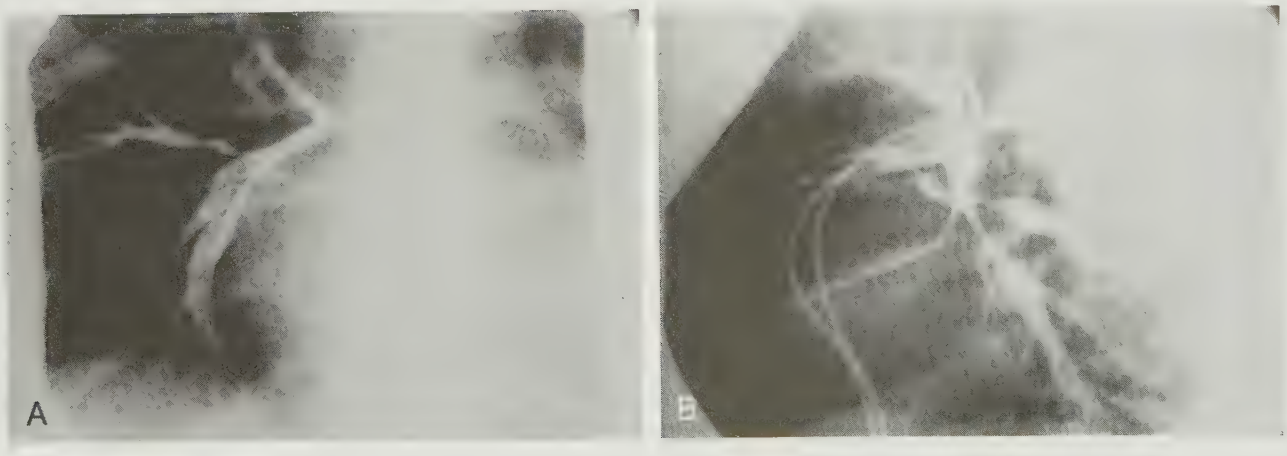

Fig. 81–28. Selective pulmonary arteriogram in a young man with Williams syndrome. (A) A right pulmonary angiogram demonstrates multiple areas of stenoses at the bifurcation of the distal arteries with varying degrees of poststenotic dilatation. (B) The lateral view of a selective left pulmonary artery injection demonstrates the symmetry in distal pulmonary arterial stenoses with Williams syndrome. There is an almost "starburst" appearance to the pulmonary arteries. Multiple stenoses were dilated by balloon, but the right ventricular and main pulmonary arterial pressures remained significantly elevated.

to the back and lateral lung fields should alert the physician to this diagnosis. Continuation of the murmur into diastole[315] may cause confusion with an incorrect clinical diagnosis of patent ductus arteriosus or pulmonary arteriovenous fistula. A family history of maternal rubella, familial congenital heart disease, or prolonged neonatal jaundice is important to consider. The phenotypic features of Noonan's or Williams syndrome are also important to note. The presence of tetralogy of Fallot or pulmonary valve stenosis should alert the pediatric cardiologist to the possibility of associated pulmonary arterial stenosis.

Natural History

The natural history of isolated pulmonary artery stenosis is generally benign.[337] However, multiple and peripheral stenoses carry a potentially poor prognosis. Orell and colleagues described complications including pulmonary hypertension, right ventricular failure, pulmonary artery thrombosis, and poststenotic aneurysmal dilatation with rupture and hemoptysis.[330] Progressive increase in the severity of pulmonary artery stenosis occurs and may be rapid. The relatively high incidence of thrombosis within the pulmonary arterial tree as the disease advances has led to the suggestion of prophylactic anticoagulation in selected cases.[313] Death in early infancy and later childhood has also been reported.[338] Prophylaxis against infective endocarditis is recommended for patients with anatomic pulmonary artery stenosis.

Treatment

Balloon Pulmonary Angioplasty

Because of the poor surgical results in the treatment of isolated pulmonary artery stenosis and complicated stenoses associated with other forms of congenital heart disease such as tetralogy of Fallot, an alternative approach to this disease was undertaken in 1980. Martin and co-workers described the first use of percutaneous transluminal balloon angioplasty to treat peripheral pulmonary stenosis in a postoperative 18-year-old after repair of pulmonary atresia with ventricular septal defect.[339] Following that report, Lock and co-workers described the use of transluminal balloon angioplasty in the treatment of newborn lambs with experimentally produced pulmonary artery branch stenosis.[215] With their laboratory experience, these same workers instituted a clinical protocol for balloon angioplasty of hypoplastic and stenotic pulmonary arteries.[218] Soon after this clinical study, several other authors reported their results with this procedure.[211,220,225,340]

The protocol for balloon angioplasty for peripheral pulmonary artery stenosis is similar to that previously described for pulmonary valve stenosis (Fig. 81–29A, B, C). There are some notable differences in technique, however. With peripheral pulmonary stenosis, a balloon diameter that is three to four times the diameter of the most stenotic segment of pulmonary artery is chosen. After proper positioning of the balloon, inflation is performed until the "waist" or "hourglass" disappears or until 4 to 6 atmospheres of pressure are achieved. The pressure is held in the balloon for a maximum of 30 seconds, unlike the rapid inflation–deflation time of less than 7 seconds used with pulmonary valvuloplasty.[341] Lock and colleagues have recommended not exceeding 6 atmospheres of pressure during inflation, since fatal pulmonary artery rupture occurred when pressure of 7 to 8 atmospheres was used.[218,342] After dilation, a second angiogram is performed by advancing an end-hole angiographic catheter over the guidewire that is left in place. Since perforation of the pulmonary artery has been reported when a straight guidewire is used, we recommend the use of the more flexible J-shaped wire. The major limitation of this procedure appears to be the inability to advance the balloon angioplasty catheter across the stenotic lumen.

The morphologic changes in the pulmonary arteries after percutaneous balloon angioplasty have been studied.[220,342] There were significant intimal and medial tears in all successful cases; at times these extended through the adventitia. At the site of the tear, a gap in the wall of the vessel representing up to 25% of the vessel circumference was commonly found. This gap was contained only by stretched adventitia. After several months, these gaps filled in with collagen and elastic fibers and healed in an open position, covered by thickened adventitia. One vessel demonstrated post-angioplasty intimal proliferation with restenosis of the lumen. Pathologic evaluation of the fatally ruptured hypoplastic left pulmonary artery revealed intimal tears and a 3 to 5 mm laceration at the rupture site.[342]

The results of balloon angioplasty for peripheral pulmonary artery stenosis have certainly been less spectacular than those for pulmonary valve stenosis. In Lock's original series, the balloon dilation was successful in five of seven patients.[218] In a later report, only five of thirteen patients had successful dilation of the stenotic segment documented by a significant drop in pressure gradient and increase in diameter of stenotic area.[220] Foker and co-workers attempted intraoperative balloon dilation of peripheral pulmonary artery stenosis in four patients with severely hypoplastic pulmonary arteries, and three patients improved.[343] Dilation angioplasty appears to increase both the vessel diameter and the blood flow through hypoplastic arteries.[218] Increasing perfusion past such vessels is unlikely to occur after a conventional operative approach. Haworth and co-workers noted that direct surgical anastomosis into a hypoplastic pulmonary artery generally uncovered stenosis distal to the mediastinum.[344] McGoon and co-workers noted that such distal stenoses are usually confined to the origins of the lobar arteries, a region out of sight for the surgeon but within reach of the balloon.[345] Thus balloon angioplasty in stenotic first- and second-generation pulmonary arterial branches appears to be the best approach to salvage hypoplastic pulmonary arteries.[218] Lock also suggested that since intra-acinar arteries of children with congenital pulmonary artery stenosis are decreased in number and the growth of these vessels appears to be greatest in the first two years of life, balloon angioplasty might need to be performed before two years of age for the best long-term results.[218,346–348]

Potential complications from this procedure include vascular rupture from an oversized balloon, perforation of a vessel from the guidewire or catheter tip, complete obstruction of the main pulmonary artery and right ventricular output during balloon dilation of proximal branch stenosis, pneumothorax, late development of aneurysms, and accelerated atherosclerosis.

Balloon angioplasty for pulmonary arterial stenosis can provide significant hemodynamic relief to a small group of patients in whom conventional operative intervention is unlikely to be successful. However, because of definite risks involved with the procedure, we routinely type and crossmatch for potential blood transfusion in all patients. In addition, we recommend that surgical and operating room "standby" be available while the balloon angioplasty procedure is being performed in the catheterization

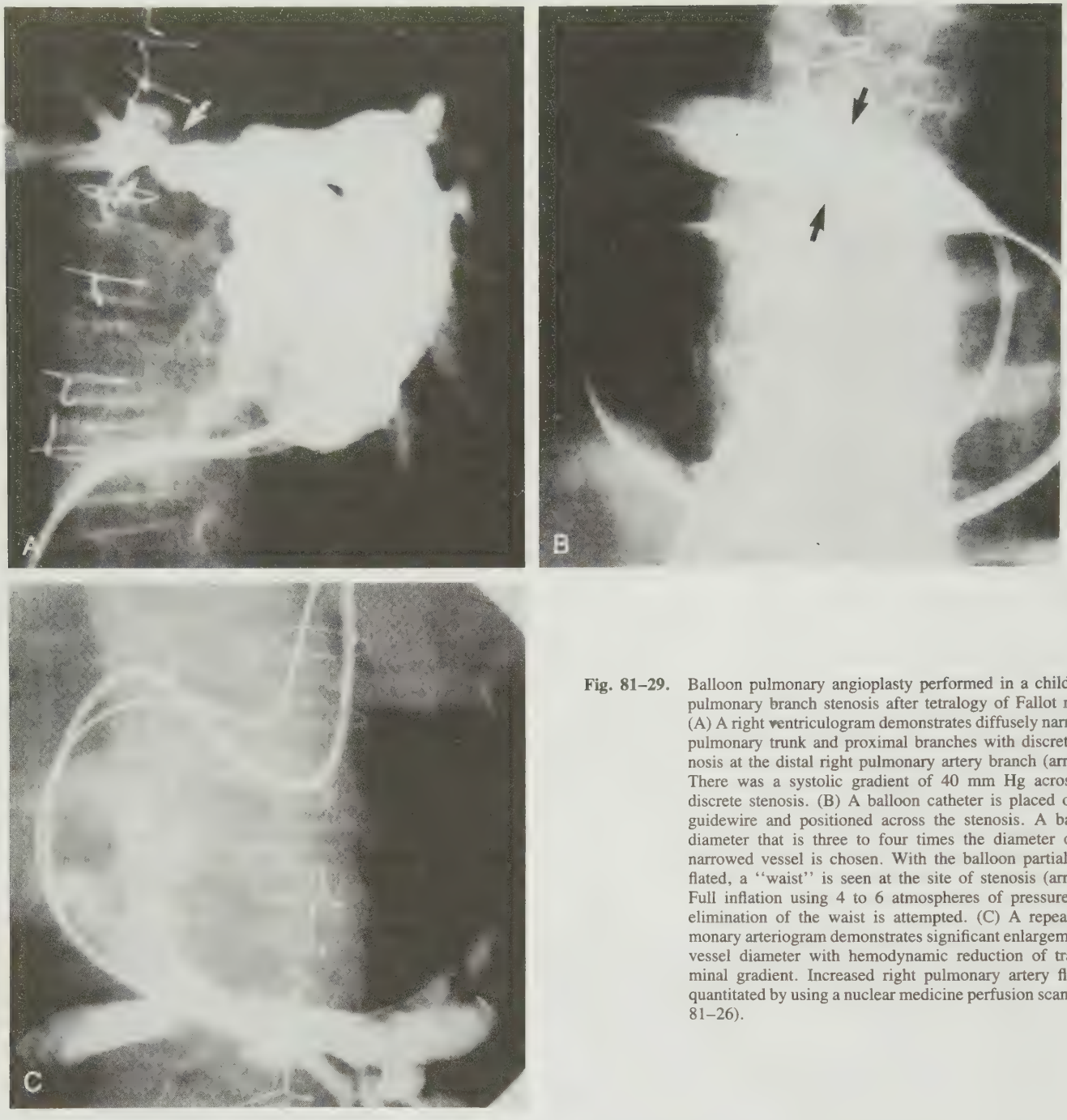

Fig. 81–29. Balloon pulmonary angioplasty performed in a child with pulmonary branch stenosis after tetralogy of Fallot repair. (A) A right ventriculogram demonstrates diffusely narrowed pulmonary trunk and proximal branches with discrete stenosis at the distal right pulmonary artery branch (arrows). There was a systolic gradient of 40 mm Hg across the discrete stenosis. (B) A balloon catheter is placed over a guidewire and positioned across the stenosis. A balloon diameter that is three to four times the diameter of the narrowed vessel is chosen. With the balloon partially inflated, a "waist" is seen at the site of stenosis (arrows). Full inflation using 4 to 6 atmospheres of pressure with elimination of the waist is attempted. (C) A repeat pulmonary arteriogram demonstrates significant enlargement of vessel diameter with hemodynamic reduction of transluminal gradient. Increased right pulmonary artery flow is quantitated by using a nuclear medicine perfusion scan (Fig. 81–26).

laboratory. We also recommend that the more distal stenotic lesions be dilated first, followed by angioplasty of the proximal obstructions in cases of multiple, peripheral, and central stenoses. This lessens the chance of inadvertent vessel perforation by passing angioplasty catheters through recently dilated vessels. Finally, it may be necessary to stage balloon dilation into separate cardiac catheterizations in individuals with bilateral multiple peripheral stenoses and those with bilateral central stenoses.

Since the results of balloon angioplasty for pulmonary arterial stenosis are not uniformly successful and long-term followup is minimal, the pediatric cardiologist has to approach the use of this procedure with some degree of caution. However, this technique has potential in the management of children with complex cardiovascular disease who otherwise might be considered inoperable. Development of techniques utilizing intravascular stents may lead to useful therapies for patients who do not respond to balloon arterioplasty.

Surgery

Surgical assistance may be attempted in patients with supravalvular pulmonary stenosis.[349] Successful relief of central obstruction in the pulmonary branches was reported initially by sev-

eral authors.[350–352] Discrete main pulmonary artery or trunk stenosis may be treated with surgery using cardiopulmonary bypass; however, the results are not entirely satisfactory.[349,353] The use of pericardial patches, woven Dacron or Gore-tex material, and tube grafts has been reported. There is no apparent prospect of surgical correction of the peripheral type of pulmonary stenosis.[313]

In our institution, the surgeon attempts relief of supravalvular or proximal pulmonary branch stenosis at the time of surgical repair of the primary congenital heart defect such as tetralogy of Fallot. If relief of obstruction is inadequate, attempts at balloon angioplasty may be made at a later date. When there is isolated pulmonary artery stenosis of significant severity, balloon angioplasty is initially performed. Surgery is reserved for cases in which the balloon dilation is unsuccessful. Transluminal balloon angioplasty appears to be the only procedure that is suitable to treat severe peripheral pulmonary arterial stenosis at this time.

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CHAPTER 82

Aortic Arch and Pulmonary Artery Anomalies

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James C Huhta

Anomalies of the aortic arch and pulmonary arteries constitute a diverse group of malformations, ranging from the cause of life-threatening airway obstruction to as yet undescribed hypothetical anomalies. A pathologic description of an anomalous right subclavian artery exists from as early as 1735 (Hunault, cited by Moes[1]), and the first pathologic description of double aortic arch was recorded in 1737 by Hommel (cited by Moes).[1] The first report of the syndrome of vascular compression produced by a double aortic arch was published by Wolman in 1939.[2] Arkin[3] recognized the radiologic appearance of double aortic arch in 1926 with a description of the radiologic features of six cases in adults in 1936. Kommerell[4] first described the roentgenologic findings of anomalous origin of the right subclavian artery in 1936, although dysphagia had long been attributed to the retroesophageal course of this vessel. (Bayford, cited by Stewart and associates[5]). Since the introduction of accurate diagnostic methods and effective surgery,[6] the variety of reported abnormalities has increased.

The range of possible deviations from normal morphology of the aortic arch and pulmonary artery is broad. The simplest abnormalities consist of abnormal origin and course of the brachiocephalic vessels. In addition, the aorta, which normally courses to the left, may deviate to the right, with or without mirror-image branching. More complex anomalies, such as double aortic arch, involve persistence of both embryonic aortic arches with hypoplasia or atresia of segments of one or the other arch.

Vascular rings are formed when one or more aortic arch abnormalities, with or without a patent ductus arteriosus or ligamentum, produce a ring that completely encircles the trachea and esophagus leading to symptoms of tracheal or esophageal constriction. A vascular "sling," which is produced by an abnormal origin and course of the left pulmonary artery[7] or abnormal origin and course of a left ductus arteriosus,[8] does not completely encircle the trachea and esophagus but may produce symptoms of tracheal or bronchial constriction. In addition, aberrant origin of brachiocephalic vessels may rarely produce symptomatic compression of the trachea[1,9] or esophagus.[10–13]

The pathology of great vessel anomalies is best appreciated in the context of the normal embryology of the aortic arch and theoretical embryopathogenesis of aortic arch and pulmonary artery abnormalities.[5,14,15] This approach can be used to explain the great variety of aortic arch and pulmonary artery anomalies. However, not all anomalies give rise to symptoms. Indeed, some postulated abnormalities have yet to be recognized and described.[5,15] Therefore the purposes of this chapter are to explore the embryology, pathologic anatomy, and clinical consequences of anomalies of the aortic arch and pulmonary artery. We will further characterize the clinical syndromes of tracheal or esophageal compression, including symptoms, physical findings, invasive and noninvasive methods of diagnosis, natural history, indications for treatment, and surgical procedures to alleviate symptoms.

EMBRYOLOGY AND EMBRYOPATHOGENESIS

The development of the aortic arch and pulmonary arteries in the human has been described in detail by Congdon[16] and by Barry,[17] and Chapter 2 of this text gives a thorough review. A brief summary of normal great vessel embryology in the human follows.

Normal

The aortic arch initially exists as paired arteries originating from the aortic sac on the ventral surface of the embryo and coursing cephalad, then turning and pursuing a caudal and dorsal course, giving rise to the paired dorsal aorta of the embryo. As the pharyngeal pouches develop, ventral and dorsal outgrowths of the aorta fuse to form the aortic arches. The aortic arches do not all exist simultaneously but develop and regress with the development of the pharyngeal pouches. However, remnants of the aortic arches persist and contribute to important parts of the mature arterial system (Fig. 82–1). By the end of the fifth week after conception, the first and second arches have regressed. Remnants of the first arch form the primordium of the internal carotid artery and the remnants of the second arch give rise to the stapedial artery, which regresses in humans. The third pharyngeal arch persists as the common carotid artery. The left fourth arch ultimately contributes to the mature aortic arch, and the right fourth arch persists as the proximal right subclavian. The fifth aortic arch may exist in humans only in rudimentary form and therefore does not contribute to the mature arterial system. However, persistence of the fifth primitive aortic arch has been reported in humans in the form of a vascular channel parallel to the definitive aortic arch.[18–20] The distal sixth arch, which appears at the end of the fifth week, regresses on the right and persists on the left as the ductus arteriosus. Ultimately, the proximal left sixth arch contributes to the main pulmonary artery, and the proximal right sixth arch contributes to the right pulmonary artery. The distal left and right pulmonary arteries develop from the postbranchial plexus and establish connection with the proximal sixth arches to complete the vascular connection between the primitive lung and the truncus. The left dorsal aorta distal to the sixth arch and from the third through the eighth somitic segment contributes to the proximal left subclavian artery and the descending aorta distal to the left subclavian artery. On the right, the third through the seventh segment of the dorsal aorta contributes to the proximal right subclavian artery, and the eighth somitic segment normally regresses.

It is possible to describe most anomalies of the aortic arch by postulating regression of a segment of the arch that would normally persist or, conversely, persistence of a segment of the arch that would normally regress.[5,14,15] Within this theoretical framework, Edwards[14] and Stewart and associates[5] described a hypothetical double aortic arch with persistence of the aortic arch on each side and with bilateral ductus arteriosi (Fig. 82–2). The anatomy of the normal left arch and each abnormality of the aortic arch are described by persistence or regression of segments of the hypothetical double aortic arch. According to this concept, the normal left aortic arch develops by regression of the eighth segment of the right dorsal aorta. The remaining elements of the right aortic arch contribute to the development of the right brachiocephalic artery and the right subclavian artery. The right ductus arteriosus normally regresses, eliminating continuity of the sixth aortic arch on the right with the aorta.

Double Aortic Arch

Just as the development of the normal left arch may be described in terms of the hypothetical double arch, abnormalities of the aortic

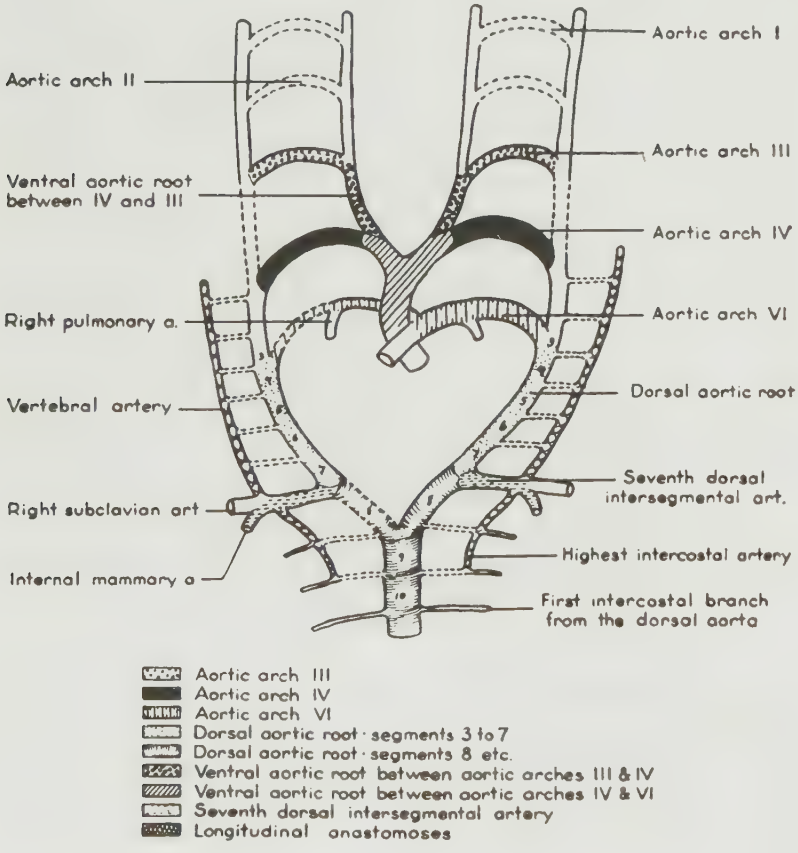

Fig. 82–1. Schematic diagram of the embryonic paired aortic arches. The aortic arches are numbered by roman numerals, and the somitic segments of the dorsal aorta are indicated by arabic numerals. Components that normally regress in the human embryo are indicated by dashed lines. (From Barry, A.: The aortic derivatives in the human adult. Anat. Rec., *111*:221, 1951.)

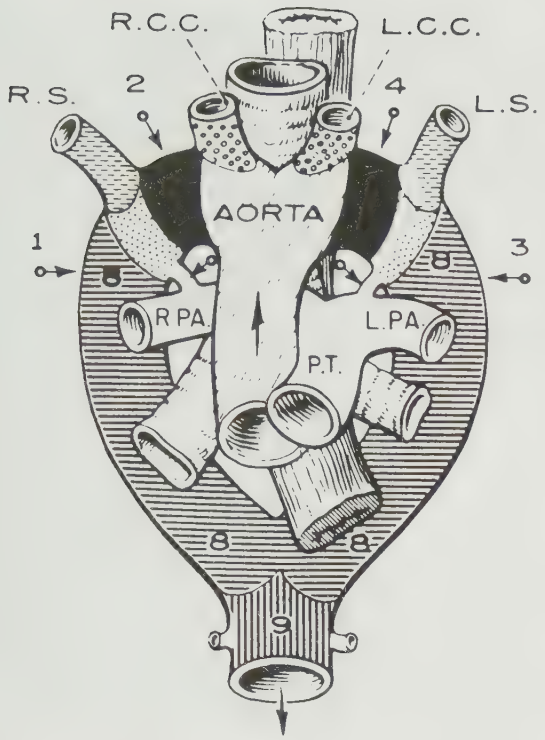

Fig. 82–2. Schematic representation of Edwards's hypothetical double aortic arch with bilateral ductus arteriosi. The ascending aorta and descending aorta are in the midline. The key to shading is that shown in Fig. 82–1. Arrows point to areas of regression, are numbered 1 through 4 for segments of the aortic arch, and are unnumbered for the ductus arteriosi. R.S. = right subclavian artery; R.C.C. = right common carotid artery; L.C.C. = left common carotid artery; L.S. = left subclavian artery; R.P.A. = right pulmonary artery; L.P.A. = left pulmonary artery; P.T. = pulmonary trunk. (From Stewart, J.R., Kincaid, O.W., and Edwards, J.E. (eds.): An Atlas of Vascular Rings and Related Malformations of the Aortic Arch System. Springfield, IL, Charles C Thomas, 1964.)

arch can also be classified by using this concept. Accordingly, double aortic arch is postulated to result from persistence of both paired dorsal aortic arches as a result of failure of regression of the right eighth somitic segment of the right dorsal aorta. The right ductus arteriosus regresses in the great majority of cases, although the ductus may persist on the right or bilaterally.[21] One or the other arch may be atretic, and atresia may theoretically occur at any segment,[5,15–17,21,22] although atresia of the segment between the ascending aorta and the left carotid has not been reported. The double aortic arch forms a complete vascular ring.[23] Persistence of the ductus arteriosus on either side is not required to complete the vascular ring in the case of double aortic arch as it is in other forms of vascular ring.

Right Aortic Arch

Right aortic arch may form by one of two mechanisms giving rise to right aortic arch with and without mirror image-branching.[5,14,15] The former occurs with abnormal regression of the left eighth dorsal aortic arch segment with persistence of the right. The ductus arteriosus almost always originates from the base of the left innominate artery. In right aortic arch without mirror-image branching, regression occurs between the left carotid and the left subclavian artery. The left subclavian artery arises from the descending aorta and courses posterior to the esophagus. In this situation, the ductus arteriosus arises from the descending aorta at the base of the left subclavian artery or from a retroesophageal diverticulum and produces a vascular ring that completely encircles the esophagus and trachea.

Anomalous Subclavian Artery

As described above, the formation of the normal left arch results from regression of the right eighth aortic arch segment. However, regression may occur between the right carotid artery and the right subclavian, giving rise to anomalous origin of the right subclavian from the descending aorta.[5,13–15] The ductus arteriosus is usually left-sided, and thus no vascular ring is formed. However, the ductus may arise from the base of the right subclavian artery or descending aorta, particularly when the descending aorta passes posterior to the esophagus and descends on the right.[24–27] This rare combination results in a vascular ring with a left aortic arch, right descending aorta, anomalous right subclavian artery, and right ductus arteriosus. A right-sided ductus arteriosus represents persistence of the distal right sixth aortic arch with regression of the distal left sixth arch.

Cervical Aortic Arch

Cervical aortic arch probably results from failure of regression of the third primitive aortic arch with regression of the contralateral arch between the carotid and subclavian arteries (fourth primitive arch).[28–30] In some cases, cervical position of the aortic arch with normal branching of the brachiocephalic arteries may merely result from failure of descent of the arch into the thorax with development.

Pulmonary Artery Anomalies

Anomalous origin of the left pulmonary artery, absent left pulmonary artery, and origin of the left pulmonary artery from the ascending aorta may all result from abnormal regression of the left proximal sixth arch. The left pulmonary postbranchial plexus, representing the vascular supply of the undivided primitive lung tissue,[16] would then establish arterial connections in one of four ways. In the case of unilateral absence of one pulmonary artery, the postbranchial plexus may establish connection to the systemic circulation by way of the distal left or right sixth arch, which would ultimately form the ductus arteriosus,[31–33] or directly to the dorsal aorta as bronchial collaterals[31] (Fig. 82–3). In some patients with origin of the right pulmonary artery from the ascending aorta, the presence of ductal tissue in the proximal right pulmonary artery implies maintenance of connection with the systemic circulation by way of the distal right sixth arch. Alternatively, origin of one pulmonary artery from the ascending aorta may result from malalignment of the conotruncal ridges.[34,35] With septation of the conotruncus, one pulmonary artery maintains connection with the ascending aorta while the other is connected to the main pulmonary artery. In patients with anomalous left pulmonary artery, arterial connection to the right pulmonary artery would occur by way of postbranchial channels between the trachea and the esophagus.[5,16,36,37] In this way, the anomalous vessel would arise from the right pulmonary artery and cross posterior to the trachea to the left hilum.

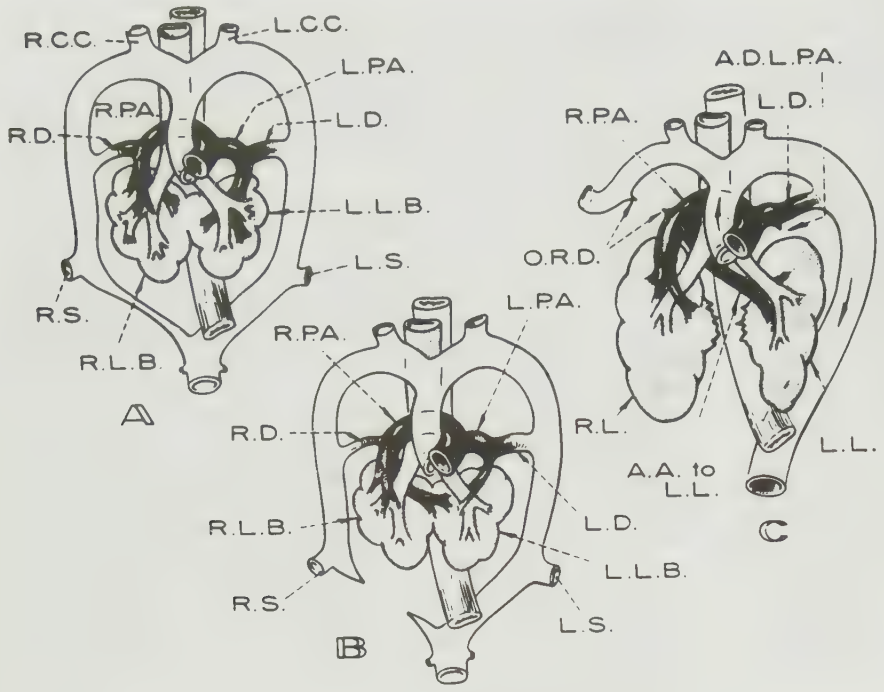

Fig. 82–3. Schematic representation of the development of the normal left pulmonary artery (A) and anomalous origin of the left pulmonary artery from the right pulmonary artery (B and C). Vessels arising from the right (R.L.B.) and left (L.L.B.) primitive lung buds normally establish connection to the proximal right (R.P.A.) and left (L.P.A.) pulmonary arteries. With anomalous origin of the left pulmonary artery from the right pulmonary artery, all or part of the vascular supply to the left lung does not establish connection to the proximal left pulmonary artery (B). Postbranchial channels persist and coalesce while maintaining connection to the right pulmonary artery (C) following division of the primitive lung buds into right lung (R.L.) and left lung (L.L.). R.D. = right ductus arteriosus; L.D. = left ductus arteriosus; O.R.D. = obliterated right ductus arteriosus; A.D.L.P.A. = atretic distal part of left pulmonary artery; R.C.C. = right carotid artery; L.C.C. = left carotid artery; R.S. = right subclavian artery; L.S. = left subclavian artery; A.A. to L.L. = anomalous artery to left lung. (From Stewart, J.R., Kincaid, O.W., and Edwards, J.E. (eds.): An Atlas of Vascular Rings and Related Malformations of the Aortic Arch System. Springfield, IL, Charles C Thomas, 1964.)

The many other possible and actual variations in aortic arch and pulmonary artery anatomy are further described by Stewart and associates[5] and by Shuford and Sybers.[15]

ETIOLOGY

Abnormalities of the aortic arch system including double aortic arch, aberrant subclavian vessels, and atresia of the sixth aortic arch have been produced in experimental animals by a number of teratogens.[38–41] Wilson[38] described the production of right aortic arch, double aortic arch, and absence of the ductus arteriosus in embryonic rats treated with azo dyes. Hodach and associates[39] produced double aortic arch by surface administration of epinephrine to chick embryos. Other catecholamines with beta-adrenergic activity also produce aortic arch anomalies when applied to the surface of chick embryos.[40] These agents also produce hypotension and tachycardia, results implying a possible hemodynamic mechanism for production of arch anomalies. The teratogenic effects of beta-adrenergic agents are potentiated by cocaine and theophylline and are attenuated by beta-adrenergic blockade.[40] Radiation exposure of mice, rat, and chick embryos in the form of roentgen rays,[42] ultraviolet light,[43] and neutron-ionizing radiation[41] also leads to the development of cardiovascular defects including aortic arch anomalies. The role of teratogenic agents in the production of aortic arch and pulmonary artery anomalies in the human is unknown.

NORMAL AND PATHOLOGIC ANATOMY

A number of classifications of aortic arch anomalies have been published.[1,5,9,15,21,44] The essential elements in any classification must include not only the side of the arch but also the origin and course of the brachiocephalic vessels, the origin of the ductus arteriosus, and the side of the descending aorta. The classifications of Stewart and associates[5] and Shuford and Sybers[15] emphasize pathologic anatomy by grouping abnormalities according to side of the aortic arch (left, right, or bilateral), origin of the brachiocephalic vessels, and site of origin of the ductus arteriosus or ligamentum arteriosus. Freedom and associates[21] have classified aortic arch and pulmonary abnormalities according to the presence or absence of vascular ring, vascular sling, or compression without formation of a vascular ring or sling. Sissman[9] has grouped abnormalities of the aortic arch by position, course, length, and size of the aorta. Each of these classifications emphasizes important aspects of anatomy and presentation of aortic arch and pulmonary artery anomalies. For the purposes of this discussion, we have adapted the classification of Stewart and associates[5] and of Shuford and Sybers[15] in describing the pathologic anatomy of aortic arch and pulmonary artery malformations. In this classification, abnormalities of the aortic arch may be divided into five groups: (1) double aortic arch, (2) right aortic arch,(3) left aortic arch with anomalous branching, (4) cervical aortic arch, and (5) pulmonary artery anomalies.

Normal Left Aortic Arch

In the simplest terms, a left aortic arch may be defined as one in which the arch courses to the left and the upper mediastinal descending thoracic aorta is to the left of the spine. Likewise, a right aortic arch could be defined as the converse of the left arch. In a normal left arch, the first branch is characteristically the right innominate artery, whereas in a left arch with anomalous branching, the right carotid artery is the first and the right subclavian artery is the last brachiocephalic artery to arise from the aortic arch and descending thoracic aorta. In a normal left arch, the aorta arises from the base of the heart to pass anterior and then to the left of the trachea. The aortic arch continues posterior and dorsal, passing to the left of the esophagus and descending in the posterior mediastinum to the left and anterior to the vertebral bodies. In the

normal left arch, the ascending aorta is the segment of the arch from the aortic valve to the origin of the innominate artery. The innominate artery arises as the first branch of the ascending aorta and passes to the right, anterior to the trachea. The innominate artery then bifurcates to form the right subclavian and carotid arteries. The second vessel to arise from the aortic arch is the left carotid. Origin of the left carotid from the innominate artery is a relatively common variation, occurring in 10 to 25% of normal patients.[45,46] When the left carotid arises from the aortic arch, the normal course of this vessel is to the left of the trachea. The third vessel arising from the aorta is the left subclavian, although the left vertebral artery may arise as the third branch in 6 to 10% of normal patients.[45,46] Distal to the origin of the left subclavian artery, the ductus arteriosus originates from the ventral surface of the descending aorta.

Double Aortic Arch

Double aortic arch is characterized by persistence of both embryonic aortic arches with separate origin of the carotid and subclavian arteries from each arch. Therefore there is no innominate artery in double aortic arch. The ascending aorta bifurcates anterior to the trachea, and each arch courses either to the left or to the right of the trachea and esophagus (Fig. 82–4). The larger of the two arches usually crosses posterior to the esophagus and joins with the other arch in the posterior mediastinum to form the unified descending aorta. Thus a complete vascular ring is formed, completely encircling the trachea and esophagus. The ductus arteriosus is almost always left sided but may originate on the right or be present on both the left and right.[5,15,21] Although the side of the ductus or ligamentum is not important in the formation of the vascular ring, the length of the ductus may affect the degree of tracheal or esophageal compression produced by the ring.

In double aortic arch, both arches are usually patent, although one arch is usually larger than the other.[5,15,22,23] When the descending aorta lies to the left of the spine, the right arch, which is more posterior than the left, is larger in approximately 70% of cases.[1,22] The right arch continues posterior to the esophagus, where it joins the left arch to continue as the descending aorta. Thus the descending aorta is usually on the left when the right aortic arch is larger. This is the most common form of double aortic arch. When the descending aorta lies to the right of the spine, the left arch is more posterior and is larger than the right in 75 to 85% of cases.[1,22] As a rule, the descending aorta is contralateral to the side of the dominant arch.

Although hypoplasia of one arch is common, segmental atresia of one arch, usually the left, occurs uncommonly.[5,15,22,23] Shuford and Sybers[15] described four subtypes of double aortic arch with segmental atresia of the left arch (Fig. 82–5). In subtype 1, atresia occurs between the left-sided ductus arteriosus and the descending

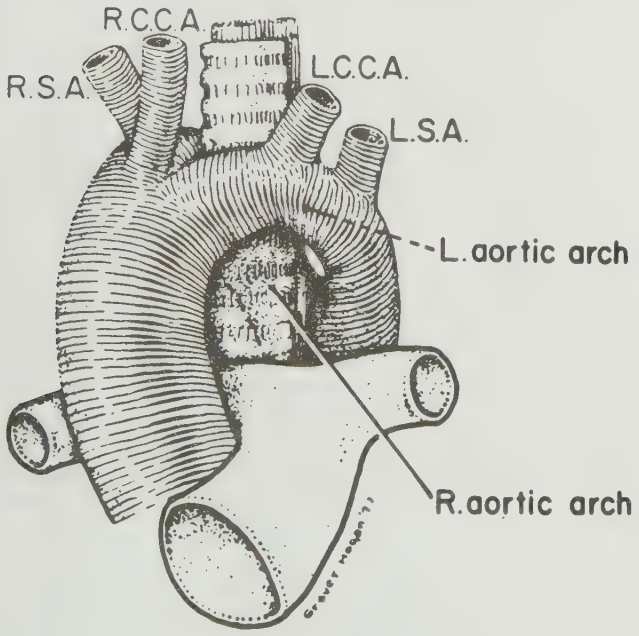

Fig. 82–4. Anatomic relationships between the trachea, esophagus, pulmonary artery, and aortic arches in double aortic arch. In this instance, the right aortic arch is larger and pursues a retroesophageal course. The vascular ring is formed by the ascending aorta anterior to the trachea, the right and left arches to either side of the trachea, and the retroesophageal right arch and descending aorta posterior to the esophagus. The ductus arteriosus or ligamentum arteriosus is not shown, since it is not an essential element of the vascular ring. R.S.A. = right subclavian artery; R.C.C.A. = right common carotid artery; L.C.C.A. = left common carotid artery; L.S.A. = left subclavian artery. (From Shuford, W.H., and Sybers, R.G.: The Aortic Arch and Its Malformations with Emphasis on the Angiographic Features. Springfield, IL, Charles C Thomas, 1974.)

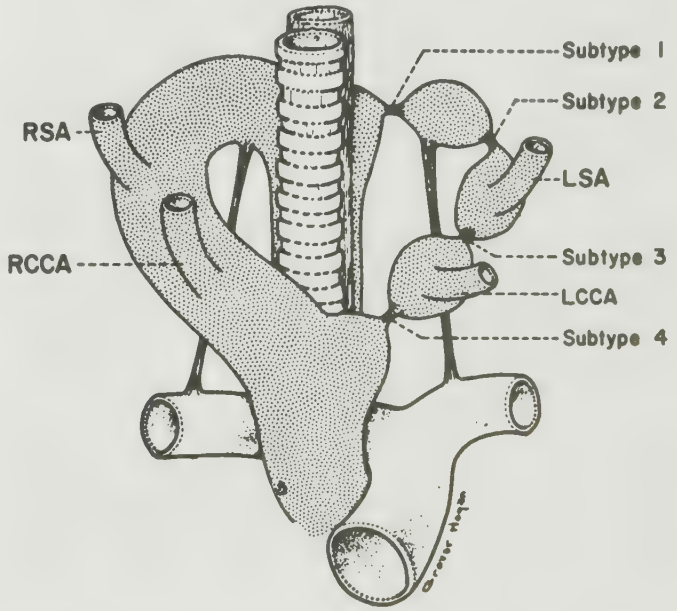

Fig. 82–5. Diagrammatic representation of double aortic arch with segmental atresia of the left arch. In subtype 1, atresia occurs between the left-sided ductus arteriosus and the descending aorta. In subtype 2, atresia occurs between the left subclavian and the left ductus arteriosus. Atresia between the left carotid artery and the left subclavian may occur (subtype 3) but is extremely rare. In subtype 4, atresia theoretically would occur between the ascending aorta and the left carotid artery but has not been reported. R.S.A. = right subclavian artery; R.C.C.A. = right common carotid artery; L.S.A. = left subclavian artery; L.C.C.A. = left common carotid artery. (From Shuford, W.H., and Sybers, R.G.: The Aortic Arch and Its Malformations with Emphasis on the Angiographic Features. Springfield, IL, Charles C Thomas, 1974.)

aorta. In subtype 2, atresia occurs between the left subclavian and the left ductus arteriosus. Subtypes 1 and 2 are rare variants of double aortic arch. Atresia between the left carotid artery and the left subclavian artery may occur (subtype 3) but is extremely rare. In subtype 4, atresia theoretically would occur between the ascending aorta and the left carotid artery. However, there has been no report of this anomaly in the literature. Double aortic arch with segmental atresia of the left arch may be difficult if not impossible to distinguish by angiography or echocardiography from various forms of right aortic arch with anomalous left subclavian artery. In addition to segmental atresia of the left arch, double aortic arch with segmental atresia of the right aortic arch has been reported.[24,25]

Double aortic arch usually occurs without associated congenital heart disease. However, associated congenital heart disease may occur in up to 22% of cases.[1] Cyanotic congenital heart disease predominates, including tetralogy of Fallot[1,5,23,47] and transposition of the great arteries.[1,48] Patients with ventricular septal defect,[1] atrial septal defect,[1,47] and true coarctation of one arch[1,5] have also been reported.

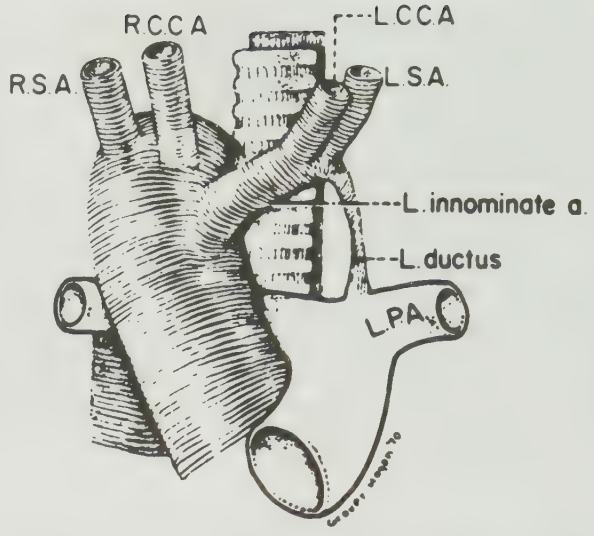

Fig. 82–6. Right aortic arch with mirror-image branching. The first branch from the ascending aorta is the left innominate artery. The ductus arteriosus typically arises from the innominate artery at the base of the left subclavian artery (L.S.A.). R.S.A. = right subclavian artery; R.C.C.A. = right common carotid artery; L.C.C.A. = left common carotid artery; L.S.A. = left subclavian artery. (From Shuford, W.H., and Sybers, R.G.: The Aortic Arch and Its Malformations with Emphasis on the Angiographic Features. Springfield, IL, Charles C Thomas, 1974.)

Right Aortic Arch

As was noted above, a right aortic arch is defined as one in which the arch courses to the right and the upper mediastinal descending thoracic aorta comes to lie to the right of the spine. Characteristically, the first branch is either the left innominate artery or the left carotid artery. Accordingly, a right aortic arch may be classified as one of two types.[49–52] In the first type, right aortic arch with mirror-image branching, the first branch of the arch is the left innominate artery. Right aortic arch with mirror-image branching of the brachiocephalic vessels is almost always associated with cyanotic congenital heart disease.

In right aortic arch with mirror-image branching, the aorta ascends anterior to the trachea and continues to the right and posterior (Fig. 82–6). The first branch is the left innominate artery, which pursues a course to the left and anterior to the trachea. The innominate artery branches to form the left subclavian artery and the left common carotid artery. The ascending aorta is often large because of the presence of associated cyanotic congenital heart disease and may originate more toward the midline than in the left aortic arch. The continuation of the arch to the right of the trachea produces deviation of the trachea to the left. The second and third branches of the arch are the right common carotid artery and the right subclavian artery, respectively. The descending aorta continues initially to the right and anterior to the vertebral bodies and then courses obliquely to the left, exiting the thorax through the aortic hiatus.

In right aortic arch with mirror-image branching, the ductus arteriosus usually arises from the left innominate artery at the origin or near the bifurcation into the carotid and subclavian. In this sense, the branching pattern of the right aortic arch is not truly a mirror image of the normal left aortic arch. However, the ductus may arise from the proximal descending aorta on the right or from a diverticulum of the descending aorta. In the latter case, the ductus arteriosus originates from a retroesophageal diverticulum (Kommerell's diverticulum) and connects to the left pulmonary artery, thus creating a vascular ring. When the ductus originates from a retroesophageal diverticulum, the descending aorta may pursue a retroesophageal course and descend on the left. In addition to left- and right-sided ductus arteriosi, cases with bilateral ductus arteriosi have been reported.[5]

In right aortic arch with anomalous origin of the left subclavian artery, there is no left innominate artery, and the first branch from the ascending aorta is the left carotid artery followed by the right common carotid artery and the right subclavian artery (Fig. 82–7). The left subclavian artery originates from the descending aorta or from a retroesophageal diverticulum of the descending aorta. In either case, a retroesophageal component is present, and the substrate for a vascular ring is present. In the great majority of cases, the ductus arteriosus is left sided and originates from the retroesophageal diverticulum and thus produces a vascular ring.[15,50] The components of the vascular ring are the ascending aorta anterior to the trachea, the right arch to the right of the trachea and esophagus, the left subclavian artery or retroesophageal diverticulum posterior to the esophagus, and the ductus arteriosus or ligamentum on the left.

As was noted above, when a retroesophageal diverticulum is present, the descending aorta may pursue a retroesophageal course and descend on the left. This condition is uncommon (25% of right aortic arch with anomalous left subclavian) and has been termed a right circumflex aorta by Hastreiter and associates.[51] Other variations in anatomy include stenosis of the left subclavian artery, isolation of the left subclavian artery, and anomalous origin of a left innominate artery.[50] Isolation of the left subclavian artery is produced by regression of the left aortic arch between the left carotid and the left subclavian and between the ductus arteriosus and the descending aorta. Thus the left subclavian may be supplied by the ductus, which is connected to the pulmonary artery. When regression occurs between the left subclavian artery and the ductus arteriosus, the left subclavian is supplied by collaterals, and the

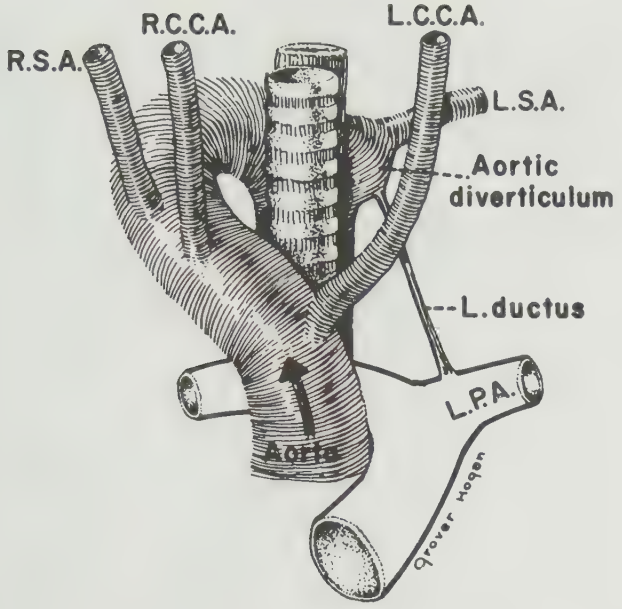

Fig. 82–7. Right aortic arch with anomalous left subclavian artery (L.S.A.) and left ductus arteriosus (L. ductus). In this illustration, the left subclavian artery and ductus arteriosus arise from a retroesophageal diverticulum (Kommerell's diverticulum) with a retroesophageal descending aorta. R.S.A. = right subclavian artery; R.C.C.A. = right common carotid artery; L.C.C.A. = left common carotid artery; L.S.A. = left subclavian artery; L.P.A. = left pulmonary artery. (From Shuford, W.H., and Sybers, R.G.: The Aortic Arch and Its Malformations with Emphasis on the Angiographic Features. Springfield, IL, Charles C Thomas, 1974.)

ductus arteriosus originates from a retroesophageal diverticulum of the descending aorta.

In right aortic arch with mirror-image branching, congenital heart disease, usually cyanotic, is present in up to 98% of patients, whereas with anomalous origin of the left subclavian, associated congenital heart disease is uncommon.[49] In tetralogy of Fallot, from 13 to 34% of patients have right aortic arch.[1,21,49,51,52] Of these, 93% have right aortic arch with mirror-image branching.[49] Likewise, the incidence of right aortic arch is relatively high in truncus arteriosus (36%)[1,21,49,51] and double outlet right ventricle (20%).[21] Right aortic arch is seen infrequently in transposition of the great arteries, being present in only 3% of cases. When present in transposition, right arch is most often associated with ventricular septal defect and pulmonary valve stenosis or single ventricle with or without pulmonary valve stenosis.[21,49] Right aortic arch may also be found in patients with tricuspid atresia (5 to 8%), ventricular septal defects (2 to 6%), and ventricular inversion with transposition (1%).[21,49,51] According to Nath and associates,[53] although congenital heart disease is uncommon, when it is present in association with right aortic arch and an anomalous left subclavian, the upper descending aorta is usually on the right, that is, there is no retroesophageal segment of the aorta. When the descending aorta takes a retroesophageal course to the left, associated congenital heart disease is unlikely.

Left Aortic Arch with Anomalous Branching

Abnormalities of origin and course of the brachiocephalic vessels may be seen in patients with a left aortic arch. Anomalous origin of the right subclavian artery from the descending aorta is the most common anomaly of the aortic arch, being present in autopsy series in 0.5% of cases.[5,12,54] The anatomy of the aortic arch is normal with the exception of origin of the right subclavian artery from the descending aorta as the last branch (Fig. 82–8). This is presumed to occur as a result of regression of the right fourth primitive aortic arch between the right common carotid artery and the right subclavian artery. The right subclavian artery originates from the descending aorta at the level of the fourth thoracic vertebra and crosses the midline posterior to the esophagus. Reports of the anomalous right subclavian artery crossing the midline between the esophagus and the trachea have been disputed.[12,13] As in right aortic arch with anomalous left subclavian artery, an anomalous right subclavian artery may also originate from a retroesophageal diverticulum termed "Kommerell's diverticulum."[4] The descending aorta usually continues to the left and anterior to the thoracic vertebral bodies. When the ductus arteriosus is left sided, as it is in most cases, there is no vascular ring. However, the ductus arteriosus may arise from the Kommerell's diverticulum and connect to the right pulmonary artery. This is usually seen in association with left aortic arch and right descending aorta and is analogous to right aortic arch with circumflex left descend.[24,26,27] This rare combination of left aortic

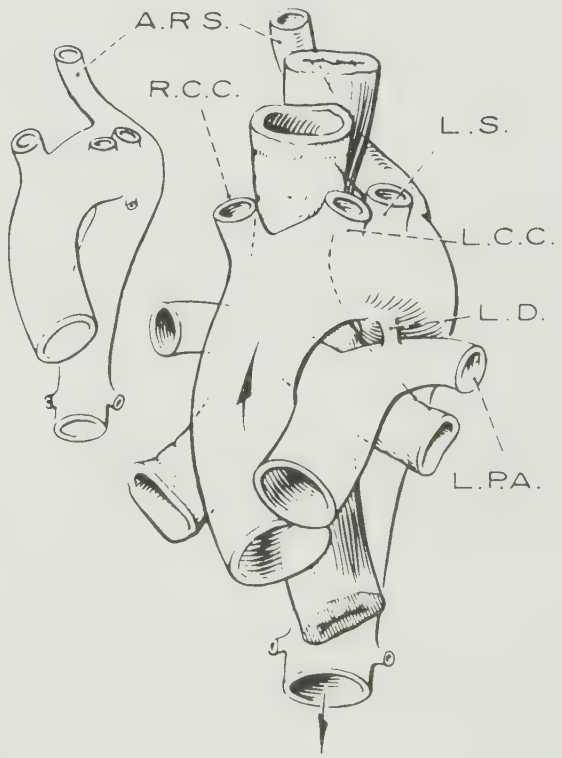

Fig. 82–8. Anomalous origin of the right subclavian artery (A.R.S.) from the descending aorta. The first branch of the ascending aorta is the right common carotid artery (R.C.C.) and the right subclavian artery arises as the last branch. Both the aortic arch and the descending aorta are on the left. L.S. = left subclavian artery; L.C.C. = left common carotid artery; L.D. = left ductus; L.P.A. = left pulmonary artery. (From Stewart, J.R., Kincaid, O.W., and Edwards, J.E. (eds.): An Atlas of Vascular Rings and Related Malformations of the Aortic Arch System. Springfield, IL, Charles C Thomas, 1964.)

arch, anomalous right subclavian artery, right ductus arteriosus, and right descending aorta produces a vascular ring.

Anomalous origin of the right subclavian artery with left arch is usually an isolated anomaly. Associations with various congenital heart defects including tetralogy of Fallot, ventricular septal defect, patent ductus arteriosus, and coarctation of the aorta have been reported.[1] In coarctation, the origin of the anomalous right subclavian artery is usually distal to the site of coarctation, which may lead to reduced blood pressure in the right arm as well as the legs. In tetralogy of Fallot, anomalous origin of the right subclavian artery has a major effect on the choice of systemic-to-pulmonary shunt performed for palliation of cyanosis. In addition, anomalous right subclavian artery has been reported to occur in 38% of patients with trisomy 21 and congenital heart disease and may be more common in trisomy 21 without congenital heart disease.[55]

The common variants in origin of the brachiocephalic vessels in left aortic arch have been noted above. These include origin of the left common carotid artery from the innominate artery and separate origin of the left vertebral artery from the aortic arch. Tracheal compression has been attributed to anomalous origin and course of the innominate artery,[1,56–62] although the role of this anomaly in producing symptoms is disputed,[63,64] and a conservative approach to diagnosis and treatment has been advocated.[65,66] Anterior indentation of the trachea is frequently noted in children without symptoms compatible with obstruction caused by an anomalous innominate artery,[67] with more severe compression in infants with tracheoesophageal fistula and in the presence of diffuse or localized tracheomalacia.[58–60,64–67] The branching pattern of the aorta is normal in patients with anomalous innominate artery. A distal origin of the innominate artery to the left of the trachea has been cited as a possible mechanism for production of symptoms of tracheal compression.[58] However, Cohen[64] found normal origin of the innominate artery in all patients undergoing surgery for airway obstruction with anterior indentation of the trachea by the innominate artery and with coexisting localized or diffuse tracheomalacia.

Cervical Aortic Arch

Cervical aortic arch is an uncommon abnormality of aortic arch development. The essential anatomy of cervical arch has been described[28] and includes (1) cervical position of the aortic arch, (2) separate origin of the carotid artery contralateral to the side of the aortic arch with anomalous origin of the subclavian artery contralateral to the aortic arch, and (3) retroesophageal descending thoracic aorta. Haughton and associates[68] have offered a somewhat expanded classification of cervical aortic arch in which the only common feature among the five types is cervical position of the aorta. In this classification, there are basically two major types: those with a contralateral descending aorta and those with an ipsilateral descending aorta. Those with a contralateral descending aorta are further subdivided into groups according to the origin and branching pattern of the carotid arteries. Those with an ipsilateral aortic arch are further divided into those with a left arch and normal branching and those with a right arch and anomalous left subclavian artery from the descending aorta.

In patients with cervical aortic arch, the ascending aorta arises from the left ventricle and ascends into the neck, usually on the right[28] (Fig. 82–9). Although less frequent, the apex of the arch may be on the left.[69–72] The arch may be as high as the second cervical vertebra[9] but usually lies at or below the third through the eighth cervical vertebrae.[1] The branching pattern of the brachiocephalic vessels is variable with separate origin of the internal and external carotid arteries on one or both sides or with a bicarotid trunk.[15,28,72] The subclavian artery on the side of the arch arises near the apex of the arch. The descending aorta enters the thorax on the side of the arch and crosses the midline posterior to the esophagus at the level of the fourth thoracic vertebral body. The subclavian artery contralateral to the arch arises from the descending aorta either directly or from a diverticulum of the descending aorta after the aorta crosses the midline. In addition, the origin of the contralateral subclavian is often stenotic, particularly when arising from a Kommerrell's diverticulum. The position of the ductus arteriosus is variable. If the ductus arteriosus arises from the descending aorta contralateral to the side of the arch, a vascular ring is formed. Associated congenital heart disease is rare, although aortic obstruction due to redundancy of the aorta has been observed.

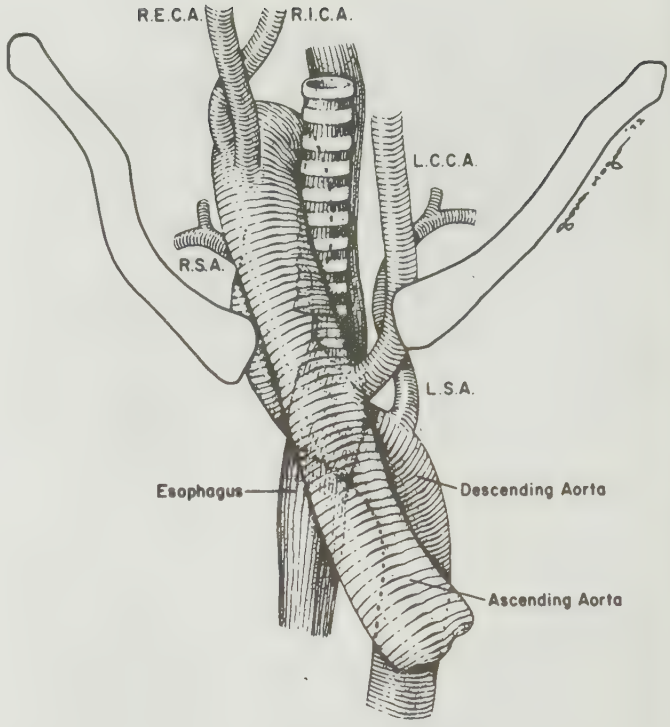

Fig. 82–9. Cervical aortic arch. The arch ascends on the right into the cervical region, then re-enters the thorax on the right. The descending aorta pursues a retroesophageal course. The right internal carotid artery (R.I.C.A.) and right external carotid artery (R.E.C.A.) have separate origins, and the left subclavian artery (L.S.A.) originates from the descending aorta. L.C.C.A. = left common carotid artery; R.S.A. = right subclavian artery. (From Shuford, W.H., and Sybers, R.G.: The Aortic Arch and Its Malformations with Emphasis on the Angiographic Features. Springfield, IL, Charles C Thomas, 1974.)

Essentially, two theories have been advanced to account for the pathologic anatomy of cervical aortic arch. Abnormal persistence of the second or third primitive aortic arch has been postulated to account for cervical position of the arch and the abnormal origin and branching of the carotid arteries.[15,28] This hypothesis would

account for separate origin of the internal and external carotid arteries as well as the cervical position of the apex of the aortic arch. An alternative hypothesis is that the cervical position of the aortic arch merely represents failure of the arch to descend into the thorax during fetal development. However, the separate origin of the internal and external carotid arteries and the anomalous origin of the contralateral subclavian artery are most easily explained by persistence of the primitive third arch on the side of the aortic arch with regression of the primitive fourth arch on the contralateral side. It is possible that abnormal persistence of the third primitive aortic arch accounts for the more common form of cervical aortic arch with abnormal origin and branching of the brachiocephalic arteries, whereas failure of descent of the aortic arch accounts for those cases with an ipsilateral descending aorta. The patient reported by Cornali and associates[29] is interesting in considering the embryopathogenesis of cervical aortic arch. In this case, where there was double aortic arch with a left cervical arch on one side and a right thoracic arch on the other, it is difficult to postulate failure of descent of the left cervical arch with coexistence of a right aortic arch in the thorax. It is more likely that the left cervical arch developed as a result of persistence of the left third aortic arch and the right arch resulted from persistence of the right eighth somitic segment of the dorsal aorta. However, although it is interesting to speculate on the embryopathogenesis of cervical aortic arch, such speculation has little bearing on the recognition and management of this rare anomaly.

Pulmonary Artery Anomalies

In addition to abnormalities of the definitive aortic arch, abnormal origin and course of the branch pulmonary arteries probably result from abnormal persistence or regression of components of the primitive aortic arch system, specifically the primitive sixth aortic arches. The pathology of anomalous origin of the left pulmonary artery, absence of a single pulmonary artery, and origin of a single pulmonary artery from the ascending aorta will be described below.

Anomalous Origin of the Left Pulmonary Artery

In addition to anomalies of the aortic arch, anomalous origin of the left pulmonary artery may produce tracheal compression by creating a "vascular sling."[7] The left pulmonary artery arises from the posterior surface of the right pulmonary artery, passes over the right main stem bronchus, then crosses the midline posterior to the lower trachea or carina and anterior to the esophagus[5,36,73] (Fig. 82–10). The anomalous left pulmonary artery then enters the hilum of the left lung and divides. The anomalous left pulmonary artery characteristically enters the left hilum at a lower level than normal. Therefore in contrast to aortic arch anomalies that produce vascular rings, the compression produced by the anomalous left pulmonary artery is on the posterior surface of the trachea and does not completely encircle the trachea and esophagus. The ductus arteriosus is left sided and connects to the main pulmonary artery.

Atresia or agenesis of the proximal left sixth arch has been postulated as the cause of this anomaly. Establishment of collateral blood flow through the postbranchial plexus to the left lung eventually results in the formation of an anomalous left pulmonary artery with connection to the right pulmonary artery. This hypothesis is supported by the finding of mixed pulmonary arterial

Fig. 82–10. Schematic representation of anomalous origin of the left pulmonary artery. The anomalous left pulmonary artery originates from the posterior superior surface of the right pulmonary artery and crosses between the trachea and esophagus in its course to the left hilum. This produces a "sling," which leads to compression of the right main stem bronchus and the lower trachea. R.C.C. = right common carotid artery; L.S. = left subclavian artery; R.S. = right subclavian artery; L.C.C. = left common carotid artery; R.P.A. = right pulmonary artery; P.T. = pulmonary trunk. (From Stewart, J.R., Kincaid, O.W., and Edwards, J.E. (eds.): An Atlas of Vascular Rings and Related Malformations of the Aortic Arch System. Springfield, IL, Charles C Thomas, 1964.)

supply to the right and left lungs, in some cases with anomalous left pulmonary artery. In one case, the arterial supply to the right upper lobe was provided by the anomalous left pulmonary artery.[74] In another case, arterial supply to the left upper lobe was provided by a left pulmonary artery in the normal position, whereas the arterial supply to the left lower lobe was provided by an anomalous left pulmonary artery.[37]

Associated congenital anomalies are common, being present in 58 to 83% of patients.[73] Approximately 40 to 50% of patients have associated congenital heart disease.[73,75–77] Persistent left superior vena cava, atrial septal defect, and patent ductus arteriosus are commonly present. An associated ventricular septal defect may be present in up to 10% of patients. Other cardiac defects that may be associated with anomalous left pulmonary artery include

tetralogy of Fallot, atrioventricular canal, common ventricle, coarctation, transposition of the great arteries, and scimitar syndrome.[76–78]

In addition to associated cardiac defects, malformations of the trachea frequently coexist with anomalous left pulmonary artery. These malformations include complete cartilaginous rings (absence of the pars membranacea), tracheomalacia, abnormal pulmonary lobulation, and bronchus suis.[73,76–78,79] Complete cartilaginous rings with absence of the pars membranacea may affect up to 50% of patients. In addition to complete rings, there is variation in number and distribution of tracheal rings.[79] The tracheal abnormalities persist after surgery and contribute significantly to the high morbidity and mortality rate in affected patients both before and after surgical repair of the anomalous left pulmonary artery. It appears that the tracheal abnormalities are primary, although some degree of deformation of the trachea may be secondary to compression by the anomalous left pulmonary artery. This is supported by the association of other primary malformations including imperforate anus, Hirschsprung's disease, biliary atresia, genitourinary defects, and anomalies of other organ systems.[73,76,77]

As was noted above, anomalous origin of the left pulmonary artery probably results from atresia of the proximal left sixth arch or failure of connection of the postbranchial plexus with the proximal left sixth arch. The anomalous left pulmonary artery would then form from postbranchial channels between the trachea and esophagus and thereby maintain connection to the right pulmonary artery[5,36,37] (Fig. 82–10). In this way, the anomalous vessel would arise from the right pulmonary artery and cross posterior to the trachea to the left hilum.

Unilateral Absence of One Pulmonary Artery

Unilateral absence of one pulmonary artery, first described by Fraentzel in 1868 (cited by Pool and associates[31]), is an uncommon congenital defect. Of 78 cases reviewed by Pool and associates,[31] 40% occurred without other associated cardiac defects. Of the remaining patients, those with absent left pulmonary artery usually had associated tetralogy of Fallot, whereas those with absence of the right pulmonary artery usually had associated patent ductus arteriosus (to the normally connected pulmonary artery). The absent pulmonary artery is usually opposite the side of the aortic arch. Ventricular septal defects are not uncommonly observed.[31] In addition, patients with atrial septal defects, patent ductus arteriosus, aortopulmonary window, subaortic stenosis with coarctation, transposition, aberrant left subclavian artery, and truncus arteriosus have been reported.[31,33]

Although the proximal pulmonary artery is absent on the affected side, the distal pulmonary artery can often be identified at surgery.[32] Thus the term "occult pulmonary artery" as suggested by Presbitero and associates[32] may be more appropriate. This vessel, which may be intrapericardial or extrapericardial, enters the hilum of the affected lung and arborizes in a way similar to a normal pulmonary artery. The arterial supply to the occult pulmonary artery may be by way of a ductus arteriosus, particularly when the affected pulmonary artery is extrapericardial, or by way of systemic collaterals. The latter may develop following ductal constriction. The contribution of bronchial circulation to arterial supply of the affected lung increases with age.[9] Evidence of initial supply to the affected pulmonary artery by the ductus arteriosus is present in the majority of cases in which the occult pulmonary artery is on the side opposite the aortic arch.[31,33]

Origin of One Pulmonary Artery from the Ascending Aorta

Origin of one pulmonary artery from the ascending aorta is a rare anomaly, occurring in 0.05% of patients with congenital heart disease.[80] Unlike truncus arteriosus, in unilateral origin of a branch pulmonary artery from the ascending aorta, there are separate pulmonary and aortic valves, and thus the term "hemitruncus" is misleading. In approximately 88% of patients, the right pulmonary artery arises from the ascending aorta and is usually the same size as, or larger than, the left pulmonary artery. Rarely, there may be stenosis at the origin of the right pulmonary artery. The vessel connects to the aorta just above the aortic valve and on the right or posterior and courses directly to the right hilum.

Overall, 75% of patients with origin of one pulmonary artery from the ascending aorta have a patent ductus arteriosus.[80] When the right pulmonary artery arises from the ascending aorta, 50% have an associated patent ductus arteriosus.[81,82] Other cardiac defects associated with origin of the right pulmonary artery from the ascending aorta include ventricular septal defect, aortopulmonary window, coarctation of the aorta, interrupted aortic arch, atrial septal defect, tetralogy of Fallot,[78,80,83,84] and contralateral pulmonary vein stenosis.[78]

Origin of the left pulmonary artery from the ascending aorta occurs as an isolated anomaly in approximately 40% of patients. In these, the aortic arch is usually on the right. In patients with associated congenital heart disease, tetralogy of Fallot is often present and is usually accompanied by a left aortic arch.[81,83,84] Patients with tetralogy of Fallot may also have severe hypoplasia of the normally connected pulmonary artery[84] or absent pulmonary valve syndrome.[81] Beitzke and Shinebourne[85] reported an unusual patient with origin of both the right and left pulmonary arteries from the ascending aorta. The main pulmonary artery did not branch and was connected to the descending aorta by a patent ductus arteriosus.

Anomalous origin of a pulmonary artery from the ascending aorta may occur as a result of abnormal conotruncal septation[34,35] or secondary to regression of the proximal right sixth arch with persistent connection of the distal right sixth arch to the aorta.[5] The former hypothesis is more plausible, since the ductus would be expected to connect the anomalous vessel to the distal aortic arch and not the ascending aorta if the distal sixth arch persisted. In addition, ductal tissue is rarely observed in the anomalously connected right pulmonary artery.

Summary of Pathology of Vascular Rings

In summary, tracheal and esophageal compression can be produced by many different variations in anatomy of the aortic arch and pulmonary artery. A complete vascular ring is formed when the trachea and esophagus are completely encircled by derivatives of the aortic arch. This always occurs in double aortic arch irrespective of the site of origin of the ductus arteriosus. Attachment of the ductus arteriosus to the pulmonary artery on the side opposite the aortic arch is always present in other forms of vascular ring. In right aortic arch with anomalous origin of the left subclavian artery, a vascular ring is almost always present and is completed by a left-sided ductus arteriosus arising from the descending aorta. Rarely, a vascular ring may exist in the presence of a left aortic

arch with anomalous origin of the right subclavian artery and with a right ductus arteriosus originating from the retroesophageal right descending aorta. Posterior esophageal compression occurs in cervical aortic arch because of the retroesophageal course of the aorta and, if the ductus is contralateral to the side of the cervical arch and ipsilateral to the descending aorta, because of a coexisting vascular ring. Tracheal and esophageal compression may be produced by origin of the left pulmonary artery from the right pulmonary artery or by connection of a left-sided ductus arteriosus to the right pulmonary artery. This has been termed a "vascular sling"[7] because, unlike vascular rings, the trachea and esophagus are not completely encircled. In both anomalous left pulmonary artery and ductus arteriosus sling, the anomalous vessel courses between the esophagus and the trachea, producing posterior and lateral tracheal compression and anterior esophageal compression.

DIAGNOSTIC EVALUATION

Aortic arch and pulmonary artery anomalies may produce life-threatening symptoms or may be asymptomatic. Symptomatic vascular rings are relatively uncommon; in addition, the symptoms of vascular compression produced by these defects are nonspecific. All too often, vascular anomalies are initially overlooked in infants with acute or chronic airway obstruction. However, a variety of noninvasive and invasive methods are available for accurate diagnosis of aortic arch and pulmonary artery anomalies. In this section, the approach to diagnosis of aortic arch and pulmonary artery malformations will be discussed and will include a review of symptoms and signs, radiologic evaluation, echocardiographic evaluation, and angiography.

Symptoms and Signs

Anomalies of the aortic arch and pulmonary artery may present with a wide range of clinical manifestations. In most intances, an abnormal course of the aorta or origin of brachiocephalic vessels is an incidental finding on chest radiographs or in the course of evaluation for suspected congenital heart disease. Difficulty in swallowing was at one time liberally attributed to anomalous origin of the right subclavian artery (dysphagia lusoria) with a retroesophageal course.[13,57,86] Although a retroesophageal right subclavian artery may very occasionally produce dysphagia,[10,11] this abnormality is clearly asymptomatic in the great majority of individuals.[12]

The most significant symptom that may occur with vascular ring is respiratory distress in the form of stridor, dyspnea, cough, and occasionally wheezing.[1,14,15,47,56] The great majority of infants and children with stridor do not have vascular rings or vascular slings as the cause of their respiratory distress.[87,88] More common causes of chronic stridor include tracheomalacia, laryngomalacia, subglottic stenosis, subglottic hemangioma, tracheal web, and foreign bodies, among many others. However, stridor and dyspnea with aortic arch and pulmonary artery anomalies may be very severe, particularly with double aortic arch or pulmonary artery sling. The severity of symptoms and the age of onset of respiratory distress are primarily determined by the degree of constriction of the trachea produced by the abnormal course of the aortic arch or pulmonary artery. Thus presentation at an early age with severe symptoms is likely with double aortic arch and pulmonary artery sling, whereas later presentation and milder symptoms are the rule with right aortic arch with an anomalous left subclavian and left ductus arteriosus. In reality, vascular rings produced by right aortic arch and anomalous left subclavian artery and left ductus arteriosus are asymptomatic in the great majority of individuals.[49] Difficulty in swallowing solid foods, or dysphagia, may be encountered in older infants and children with vascular rings.

The occurrence of sudden episodes of apnea with cyanosis in patients with tracheal compression has been termed "reflex apnea."[62] These episodes can ultimately lead to death; Fearon and Shortreed[62] and others[64] have concluded that apneic episodes should lead to early surgical intervention. However, it is important to exclude other causes of apnea in affected infants, particularly those with lesions that usually do not produce significant tracheal compression, to avoid unnecessary thoracotomy.

Findings on physical examination of symptomatic infants are those of severe respiratory distress and do not otherwise suggest the presence of a vascular anomaly. Additional physical findings may be present in patients with associated congenital heart disease. These are specific for the associated defect, such as cyanosis in tetralogy of Fallot, and do not ordinarily imply the existence of vascular anomalies. However, in coarctation of the aorta, a reduced right arm pulse in addition to reduction in leg pulses suggests the presence of an anomalous right subclavian artery arising below the site of coarctation. Since the left subclavian artery can occasionally be stenotic in coarctation, it is possible to have low-volume pulse in all extremities, making routine carotid palpation a necessity. Likewise, a pulsatile mass in the neck with a thrill and systolic murmur clearly suggests the possibility of a cervical aortic arch. Loss of femoral artery pulses on compression of the mass is pathognomonic of cervical aortic arch.[28]

Radiologic Examination

For many years, chest radiography and esophagography have been the primary diagnostic modalities used to confirm or exclude aortic arch anomalies in patients with a compatible history.[5,15,46,49,89] The anteroposterior chest radiograph is most useful in determining the laterality of the aorta. In addition to demonstrating the side of the aortic arch, the course of the descending aorta can usually be determined. In left aortic arch, the density of the aortic arch can be seen to the left of the trachea and produces rightward deviation of the trachea as the arch passes to the left and posterior. This deviation of the trachea can be identified in most patients, although tracheal deviation may be obscured by generous thymic tissue in infants. Nonetheless, deviation of the trachea to the right usually implies the existence of a left aortic arch, whereas tracheal deviation to the left is the rule in right aortic arch (Fig. 82–11). In the normal left aortic arch, the oblique course of the descending aorta along the left margin of the vertebral bodies identifies the descending aorta as left descending. In right aortic arch or left aortic arch, the descending aorta may be seen to cross to the contralateral side and thus represents a "circumflex aorta," and a vascular ring may be present.

Cases of double aortic arch with dominant left arch may have tracheal deviation to the right without other evidence of the right arch on chest radiography. However, abnormal tracheal deviation in double aortic arch may not be apparent because of generous thymic shadows. In addition, frank tracheal constriction may be recognized in double aortic arch by narrowing or obliteration of the distal tracheal air column (Fig. 82–12). A descending aorta

Fig. 82–11. Anteroposterior chest radiograph of a patient with right aortic arch and anomalous left subclavian artery. The aortic arch produces deviation of the trachea to the left. The side of the descending aorta cannot be clearly identified in this radiograph.

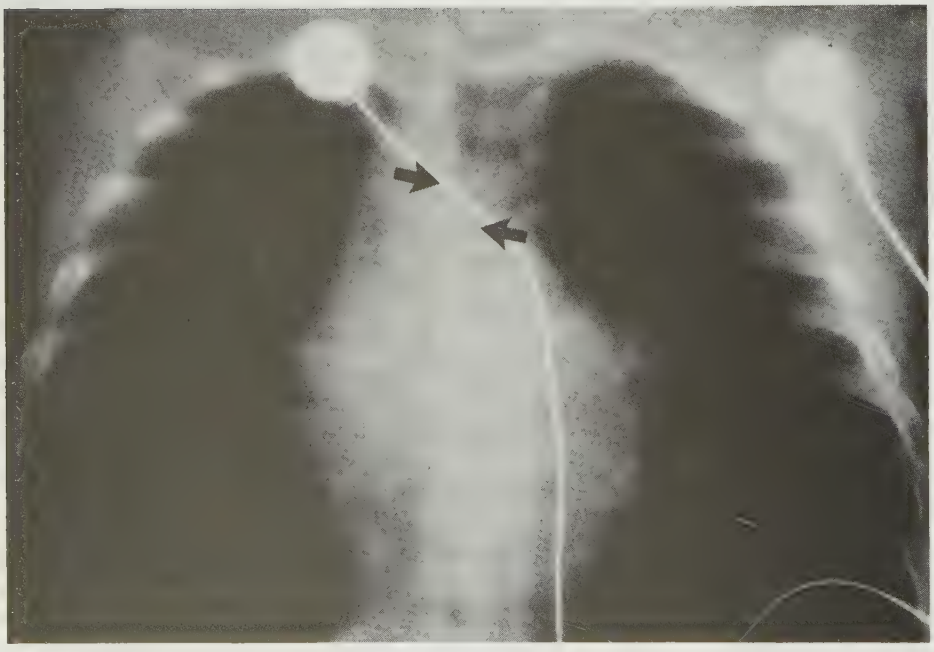

Fig. 82–12. Anteroposterior chest radiograph of a one-month-old patient with severe respiratory distress and double aortic arch. Note the bilateral hyperinflation in addition to severe constriction of the trachea on both the right and the left (arrows).

contralateral to the side of the dominant aortic arch is usually seen in double aortic arch.

Other inferences as to the type of aortic arch anomaly may be made on the basis of the presence of aortic enlargement, an abnormal cardiac silhouette, or reduced pulmonary vascular markings. In patients with cyanotic congenital heart disease, the right aortic arch is likely to have a mirror-image branching pattern, and a vascular ring is very unlikely. Likewise, a right aortic arch without findings compatible with congenital heart disease is likely to have an anomalous left subclavian artery, and the substrate for a vascular ring exists. With pulmonary artery sling, the chest radiograph shows hyperinflation on the right, the left, or bilaterally secondary to main stem bronchus obstruction. If obstruction is severe, atelectasis may be seen, particularly on the right.

Although sometimes useful, lateral chest radiographs may be normal in the presence of significant abnormalities of the aortic arch or pulmonary arteries. Anterior tracheal indentation has been noted in some patients with anomalous innominate artery,[58,59,62] although Swischuk[63] has emphasized that anterior tracheal indentation is commonly observed in normal children on lateral chest radiographs.

Although chest radiography may provide useful information in patients with suspected aortic arch anomalies, the mainstay of noninvasive diagnosis has been barium esophagography.[5,15,46,49,89] A comprehensive review of findings on esophagography has been provided by Stewart and associates,[5] Shuford and Sybers,[15] and Neuhauser.[44] The barium study should be interpreted from fluoroscopy or cine films. Both anteroposterior and lateral views are useful in describing abnormalities that may be present. In anteroposterior views, the oblique course of an anomalous left or right subclavian can be seen as the anomalous artery indents the barium-filled esophagus (Fig. 82–13). Bilateral indentations of the esophagus are often seen in double aortic arch in the anteroposterior projection, the larger arch producing a deeper, more superior indentation (Fig. 82–14). Berdon[89] has divided findings on lateral esophagography into four patterns. A large posterior indentation of the barium-filled esophagus with anterior tracheal indentation is seen in double aortic arch and right or left aortic arch with a retroesophageal descending aorta, anomalous subclavian, and a ductus arteriosus contralateral to the side of the aortic arch (Fig. 82–14 and Fig. 82–15). A shallow posterior indentation is produced by an anomalous subclavian artery without a ductus arteriosus contralateral to the arch (Fig. 82–13). Anterior indentation of the trachea or straightening of the trachea is not seen in this group, since the ductus is on the side of the arch and there is no vascular ring with compression. As was noted above, anterior tracheal indentation may be seen with innominate artery compression of the trachea. In these patients, barium esophagography is normal. The last group consists of patients with pulmonary artery sling with anterior indentation of the esophagus. In most instances, with a combination of plain chest radiography and esophagography, the type of vascular anomaly can be established. However, confusion can exist when findings are not characteristic, and conventional angiography or digital angiography should be performed when surgery is contemplated.

Echocardiographic Examination

Two-dimensional echocardiography has become a useful noninvasive method both to establish the laterality of the aortic arch and descending aorta and to determine the origin of the brachiocephalic vessels from the aorta.[90–94] In addition, normal bifurcation of the main pulmonary artery into left and right pulmonary arteries is usually easily demonstrated by two-dimensional echocardiography, effectively excluding pulmonary artery sling or absence of either branch pulmonary arteries or anomalous origin of one pulmonary artery from the ascending aorta.[84,90,95–97] The echocardiographic diagnosis of the majority of abnormalities of the aortic arch and pulmonary artery that would produce a vascular ring depends on demonstrating either absence of a normal right innominate artery or abnormal origin of the left pulmonary artery or ductus arteriosus ligamentum.

Accurate demonstration of aortic laterality and branching of the

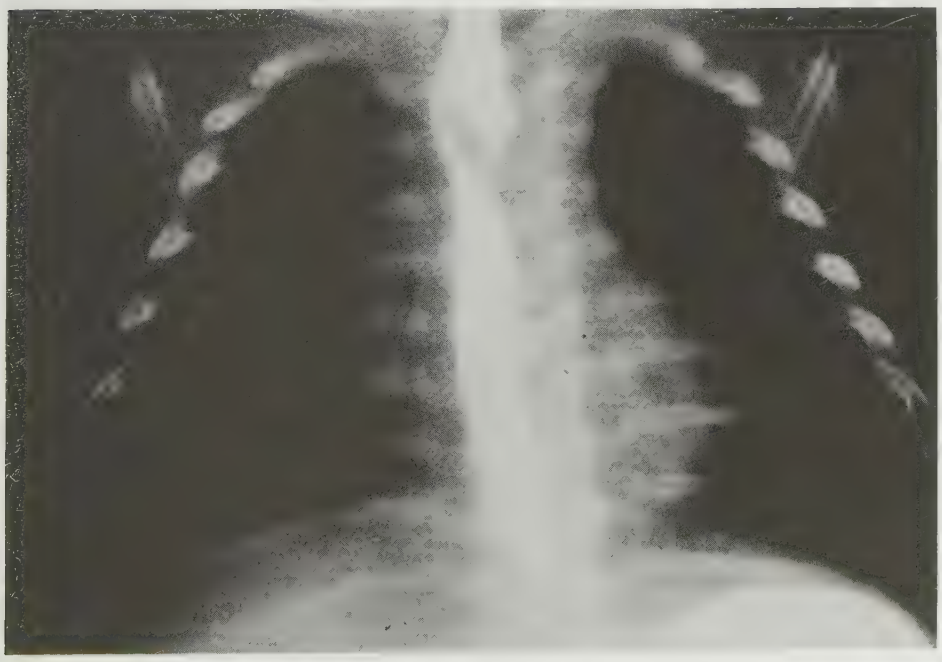

Fig. 82–13. Typical findings on barium esophagography in a patient with tetralogy of Fallot, left aortic arch, and anomalous right subclavian artery. In the anteroposterior projection, the retroesophageal right subclavian artery produces an oblique defect from left inferior to right superior.

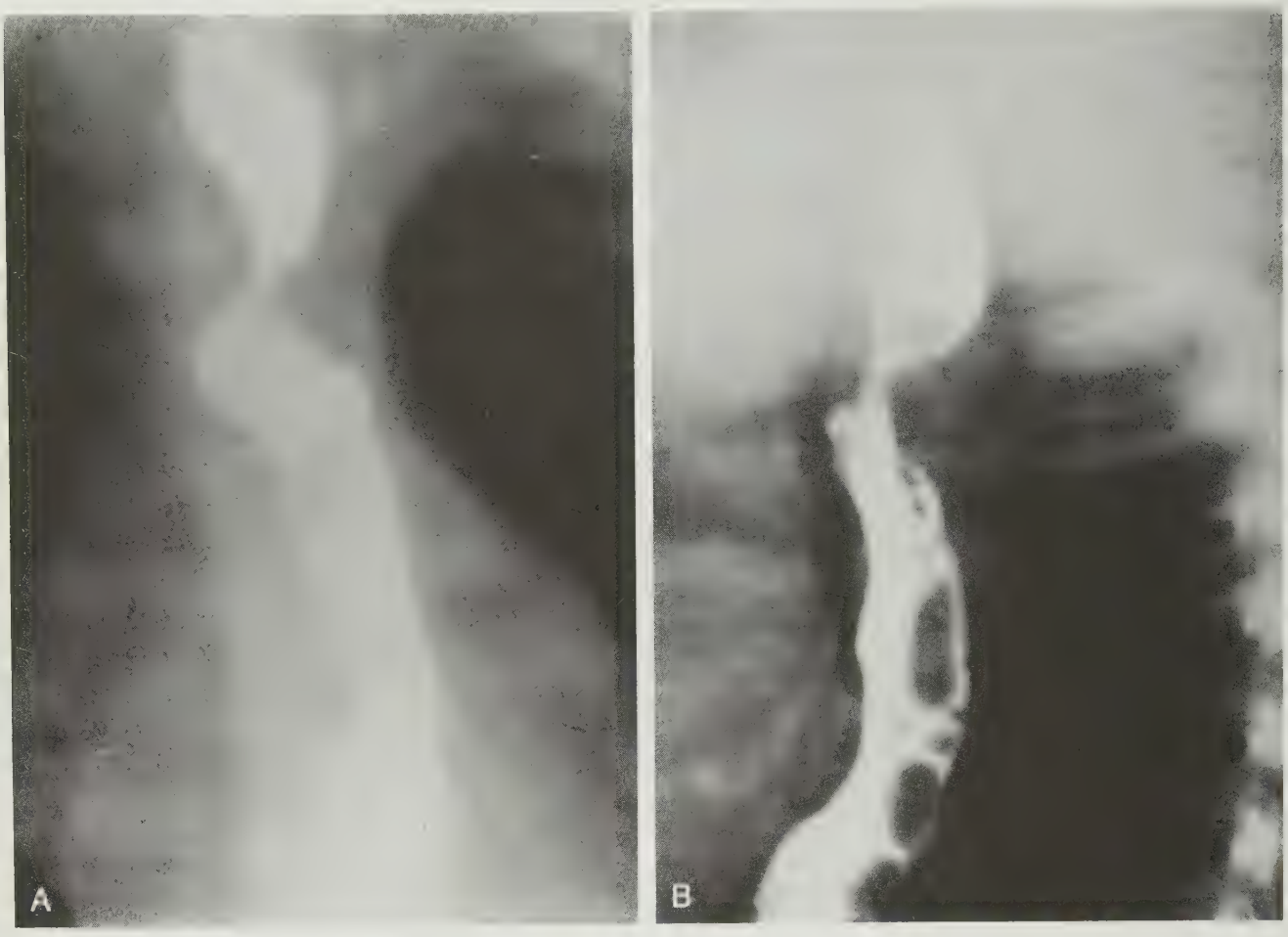

Fig. 82–14. The classic appearance of double aortic arch on barium esophagography in the anteroposterior projection is illustrated in part A. The double arch produces bilateral indentations on the upper esophagus. In part B, near-complete obstruction of the esophagus is produced by posterior compression of the esophagus by the retroesophageal portion of the arch.

aorta can be obtained only by employing a segmental approach to examination of the aortic arch as described by Huhta.[90] In this method, the ascending aorta is visualized from the suprasternal notch in a coronal plane. By directing the transducer to the right with clockwise rotation, the origin of the right innominate artery as the first branch of the ascending aorta identifies the arch as a left arch (Fig. 82–16). Normal branching of the right innominate artery excludes anomalous origin of the right subclavian artery. Clockwise rotation of the transducer and scanning to the left and posterior bring the transverse arch with the origin of the left carotid artery and left subclavian artery into view. From a high left parasternal position, scanning in the sagittal plane identifies the descending aorta to the left of the esophagus and trachea. Visualization of the esophagus may be aided by having the patient swallow a carbonated beverage or infant formula. The examination is completed by scanning from a subcostal position with visualization of the descending aorta on the left.

In right aortic arch, the first vessel to arise from the aorta courses to the left and is identified by counterclockwise rotation of the transducer. If this vessel branches to form a left subclavian artery and a left carotid artery, then mirror-image branching is present (Fig. 82–17). Scanning to the right reveals the descending aorta. Right aortic arch with mirror-image branching can be identified correctly in most patients by demonstrating a left innominate artery that branches to form a left carotid and a left subclavian with a descending aorta that courses to the right of the trachea.[90,91] However, if branching of the left innominate artery does not occur, then an anomalous left subclavian artery should be suspected, and the substrate exists for a vascular ring (Fig. 82–18). With careful examination, the anomalous left subclavian artery can be demonstrated arising from the descending aorta or from a diverticulum of the descending aorta in many cases. When patent, the left-sided ductus arteriosus can be visualized or demonstrated by pulsed Doppler sampling in the pulmonary artery (Fig. 82–19). Correct identification of vascular ring resulting from a right aortic arch with an anomalous left subclavian artery and left ductus arteriosus has been reported.[90,94] In double aortic arch with both arches patent, a characteristic coronal scan from the suprasternal notch is produced.[90,91,93] The dominant arch can often be identified, and the course of each arch can be established (Fig. 82–20).

Accurate diagnosis of anomalous left pulmonary artery can be made by scanning from both suprasternal notch and parasternal short-axis views and from the subxiphoid view. Yeager and associates[95] have reported successful identification of this anomaly

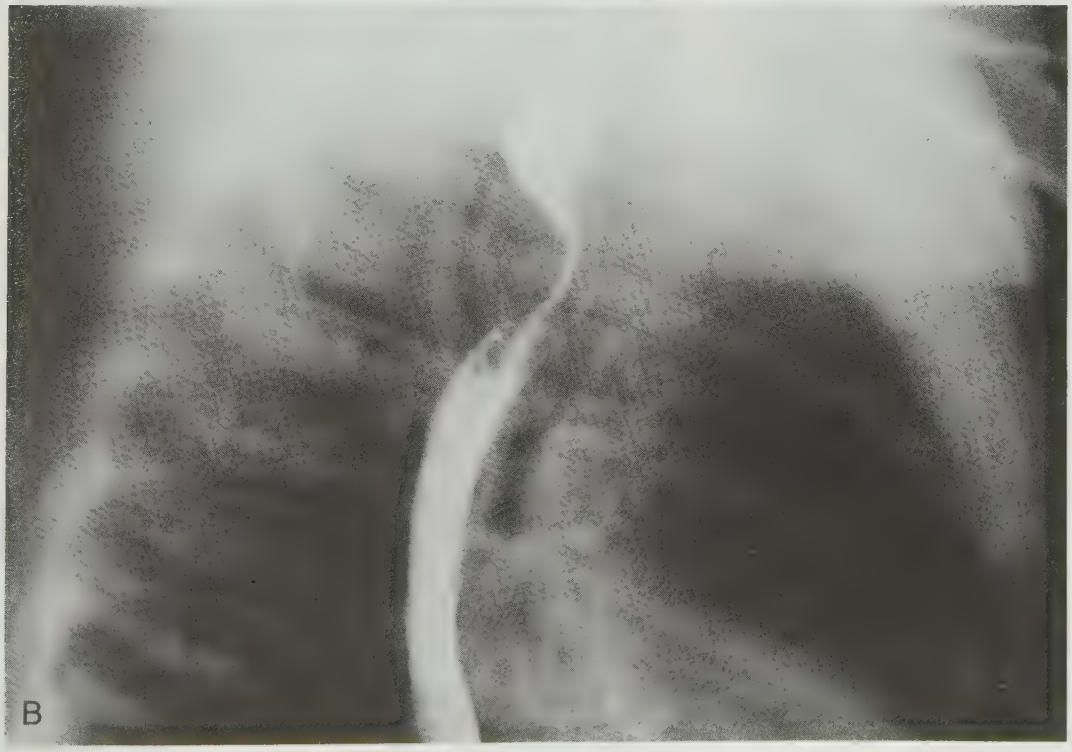

Fig. 82–15. Anteroposterior (A) and lateral (B) barium esophagograms in right aortic arch and anomalous left subclavian artery. The retroesophageal origin and course of the left subclavian artery are demonstrated by the oblique defect on the anteroposterior esophagogram (A). The presence of either a retroesophageal aorta or a retroesophageal diverticulum of the descending aorta is suggested by the large posterior defect on the lateral esophagogram (B).

Fig. 82–16. Suprasternal notch echocardiogram in the coronal plane in left aortic arch demonstrating normal branching of the right brachiocephalic artery (upper panel) to form the right carotid artery (RCA) and right subclavian artery (RSA). Anomalous origin of the right subclavian artery is suggested by the absence of branching (lower panel) of the first vessel to arise from the ascending aorta to the right (RCA). Ao = aorta. (From Huhta, J.C.: Pediatric Imaging/Doppler Ultrasound of the Chest: Extracardiac Diagnosis. Philadelphia, Lea & Febiger, 1986.)

Fig. 82–17. In right aortic arch with mirror-image branching, suprasternal notch echocardiography reveals the first branch of the aorta to the left (upper panel). This vessel, the left brachiocephalic artery, divides to form the left carotid artery (LCA) and the left subclavian artery (LSA). Counterclockwise rotation of the transducer from the coronal plane to the sagittal plane (lower panel) reveals the descending aorta (DAo) to the right of the trachea and spine and the remaining brachiocephalic vessels. Ao = aorta; IV = innominate vein; RCA = right carotid artery; RSA = right subclavian artery; AAo = ascending aorta. (From Huhta, J.C., Gutgesell, H.P., Latson, L.A., and Huffines, F.D.: Two-dimensional echocardiography of the aorta in infants and children with congenital heart disease. Circulation, *70*:417, 1984.)

Fig. 82–18. Suprasternal notch echocardiogram in a patient with right aortic arch and anomalous left subclavian artery. Scanning to the right in the sagittal plane (upper panel) reveals the ascending aorta (AAo) and descending aorta (DAo) coursing to the right. In the coronal plane (lower panel), absence of branching of the first branch of the aorta (Ao) to the left suggests anomalous origin of the left subclavian artery. A Kommerell's diverticulum (K) is seen in a retroesophageal location. RCA = right carotid artery; RSA = right subclavian artery; LCA = left carotid artery; IV = innominate vein. (From Huhta, J.C.: Pediatric Imaging/Doppler Ultrasound of the Chest: Extracardiac Diagnosis. Philadelphia, Lea & Febiger, 1986.)

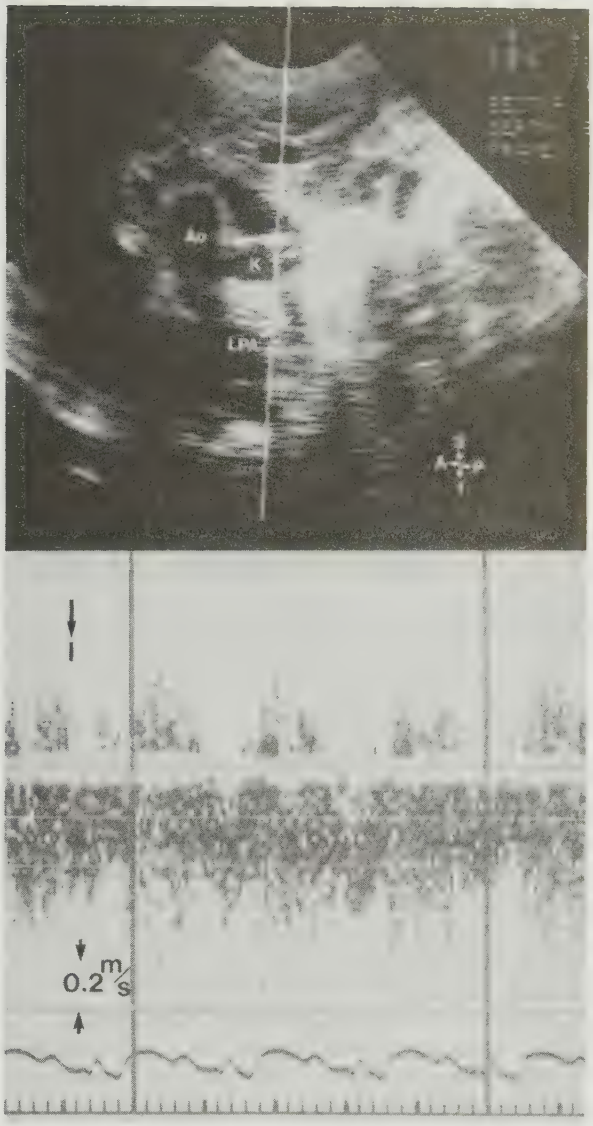

Fig. 82–19. The vascular ring is completed by demonstration of a patent ductus arteriosus on the left in the patient from Fig. 82–18. Pulsed Doppler sampling at the base of the left subclavian artery (upper panel) at its origin from the Kommerell's diverticulum (K) reveals continuous ductal flow away from the transducer toward the left pulmonary artery (LPA). Ao = aorta; m/s = meters per second. (From Huhta, J.C.: Pediatric Imaging/Doppler Ultrasound of the Chest: Extracardiac Diagnosis. Philadelphia, Lea & Febiger, 1986.)

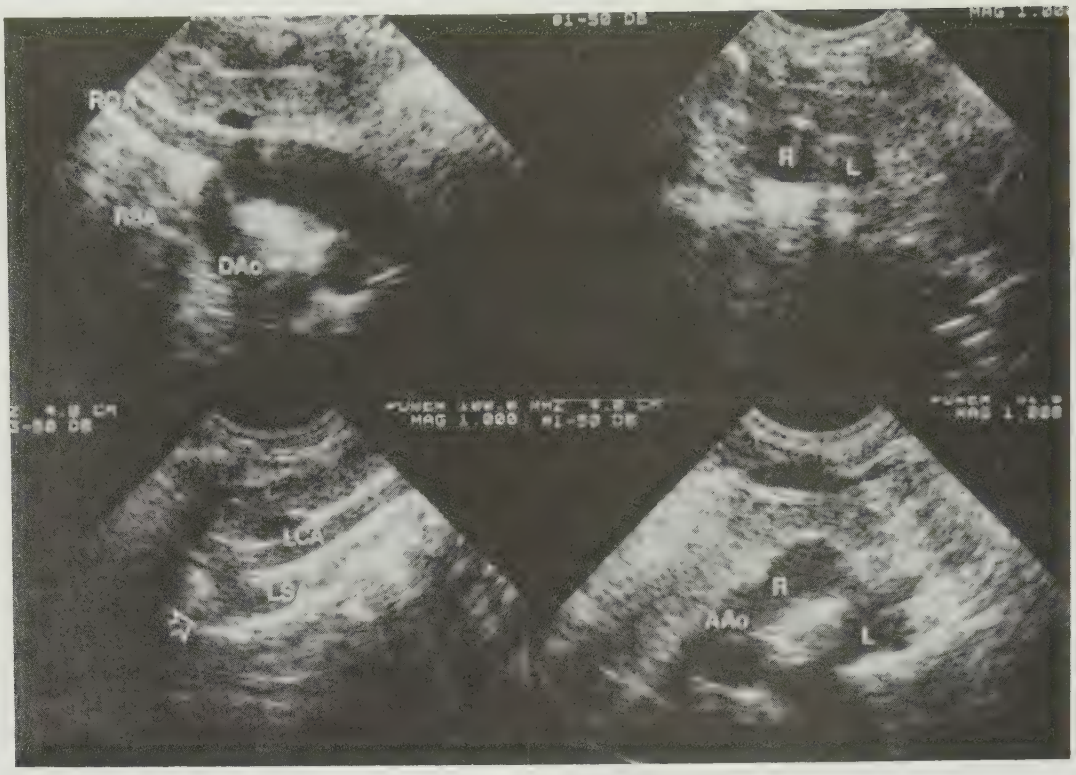

Fig. 82–20. Echocardiographic appearance of double aortic arch from the suprasternal notch. In the sagittal plane, the right aortic arch (upper left) and the left aortic arch (lower left) are demonstrated with separate origin of the carotid and subclavian arteries on each side. Scanning anterior in the coronal plane (upper right) reveals the characteristic bilateral echolucencies of double aortic arch. The right aortic arch (R) appears larger than the left aortic arch (L) in both the sagittal and coronal views. Scanning in the sagittal plane from right to left (lower right) reveals the complete vascular ring encircling the trachea and esophagus. RCA = right carotid artery; RSA = right subclavian artery; DAo = descending aorta; LCA = left carotid artery; LSA = left subclavian artery; AAo = ascending aorta.

in four of five infants known to have anomalous left pulmonary artery. Two echocardiographic features must be present to fulfill the diagnosis of anomalous left pulmonary artery. First, the normal origin of the left pulmonary artery from the main pulmonary artery in the short-axis plane must be absent. Scanning in the short-axis plane demonstrates the right pulmonary artery originating from the main pulmonary artery. However, the left surface of the main pulmonary artery is smooth without branching (Fig. 82–21). Second, origin of the left pulmonary artery from the right pulmonary artery must be established. In the suprasternal notch plane, an arterial branch can be seen to arise from the posterior surface of the right pulmonary artery. This vessel can be followed by scanning in the coronal plane and posterior to the usual plane of the right pulmonary artery. The vessel continues to the left and posterior to the trachea but anterior to the esophagus to enter the hilum of the left lung. The echocardiographic features of unilateral absence of a pulmonary artery and origin of one pulmonary artery from the ascending aorta have been described.[96,97]

Using the approach described above, Huhta and colleagues examined 22 patients with stridor and correctly identified a vascular ring in eight patients with no false-positive or false-negative diagnoses.[98] The vascular ring was the result of double aortic arch in five infants and right aortic arch with anomalous left subclavian artery and left ductus arteriosus or ligamentum arteriosus in three infants. The anatomy of the ring was confirmed at surgery in all cases. In four infants, surgery was performed on the basis of conventional noninvasive methods and echocardiography without angiography. Therefore it appears that when a vascular ring is suspected, the diagnosis can be made and sufficient anatomic detail can be provided by echocardiography to plan surgery. However, angiography is particularly useful in the unusual patient with a left arch and retroesophageal descending aorta and right ductus, since this form of vascular ring may be difficult to diagnose confidently using echocardiography alone. In addition, right aortic arch with a retroesophageal left subclavian and left ductus cannot be confidently distinguished from double aortic arch with atresia of the left arch between the left carotid and left subclavian by echocardiography or angiography. However, this distinction is not critical to surgical planning.

Angiography and Catheterization

The majority of aortic arch and pulmonary artery anomalies may be correctly identified by using a combination of standard chest radiography, barium esophagography, and two-dimensional echocardiography.[99] Certainly, when the suspected anomaly is minor, is unlikely to account for the patient's symptoms, or is minimally symptomatic, further invasive study is generally not indicated. However, greater anatomic detail than is provided by noninvasive methods may be necessary for surgical planning in patients who are significantly symptomatic. Angiography may be performed by using standard cineangiographic techniques or by using digital subtraction angiography.[15,18,90,11] The anatomy of the

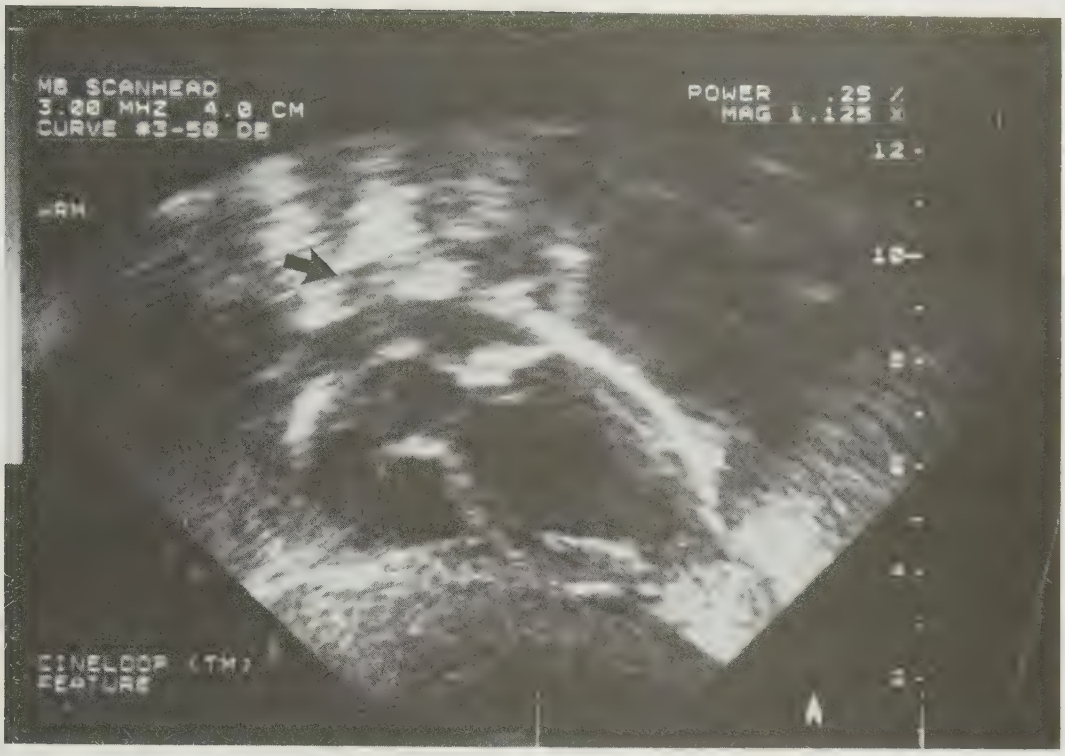

Fig. 82–21. Subxiphoid scan in a patient with anomalous origin of the left pulmonary artery from the right pulmonary artery. This scan demonstrates the absence of normal origin of the left pulmonary artery from the main pulmonary artery with posterior origin of the left pulmonary artery from the right (arrow). The course of the left pulmonary artery posterior to the trachea is also demonstrated from the subxiphoid scan.

aortic arch and descending aorta must be clearly demonstrated in addition to identifying the sequence of opacification of the brachiocephalic vessels. Standard anteroposterior and lateral projections may be used. However, in most cases, left or right oblique views with the addition of cranial angulation should be used to separate overlying structures and demonstrate the origin and course of the brachiocephalic vessels. Successful opacification of the aorta may be obtained with left ventriculography by venous catheterization with transseptal left heart catheterization, or by retrograde arterial catheterization. However, particularly when there is coexistent congenital heart disease, the best definition of aortic anatomy is obtained with aortic angiography. Digital subtraction angiography alone may provide excellent definition of aortic anatomy but does not allow cineangiographic demonstration of branching sequence. In addition, conventional catheterization provides an opportunity to study the presence and severity of associated heart disease. Use of a combination of these two methods, currently available in many cardiac catheterization laboratories, may prove to be the best approach to invasive imaging of aortic arch anomalies. The angiographic appearance of specific aortic arch and pulmonary artery anomalies is described in the following section.

CLINICAL SYNDROMES: COURSE, TREATMENT, AND PROGNOSIS

Among the many reported aortic arch and pulmonary artery malformations, a relative few account for the great majority of defects that are clinically recognized. The clinical features of these more common anomalies of the aortic arch and pulmonary artery are discussed below.

Left Aortic Arch, Aberrant Right Subclavian Artery

Left aortic arch with anomalous origin of the right subclavian artery is the most common aortic arch malformation noted on postmortem examination. The incidence of this abnormality in the general population is approximately 0.5%.[14] The left arch has a normal origin and course, but the right subclavian artery arises as the last branch of the arch and courses posterior to the esophagus. This occurs presumably as a result of abnormal regression of the embryonic right fourth aortic arch. The great majority of patients with anomalous right subclavian artery are asymptomatic, and the abnormality is discovered incidentally at esophagography for other conditions such as gastroesophageal reflux. In addition, anomalous right subclavian artery is frequently demonstrated on angiography in patients with congenital heart disease.[1] An anomalous right subclavian artery is often seen in patients with tetralogy of Fallot and left aortic arch[1] and would therefore have a significant bearing on the choice of systemic-to-pulmonary artery shunt employed for palliation of cyanosis. In addition, anomalous right subclavian artery may be present in patients with coarctation of the aorta[1,5,15] and often arises distal to the site of coarctation. In these patients, the blood pressure in the right arm and legs would not reflect the coarctation gradient. Likewise, when the anomalous right subclavian artery arises distal to the coarctation, rib notching will be observed only on the left, whereas when the anomalous right subclavian artery arises proximal to the coarctation, bilateral rib notching is observed.[1]

Clearly, most patients with anomalous right subclavian artery are asymptomatic,[12] although some older children and adults may occasionally experience dysphagia.[10,11] In these uncommon patients, surgical division and reimplantation of the anomalous subclavian artery may produce relief of dysphagia. However, prior to performing surgery, a thorough search should be made for other abnormalities that might account for the patient's symptoms.

Routine chest radiography does not demonstrate this anomaly, but barium esophagography is diagnostic. The oblique course of this vessel posterior to the esophagus in the anteroposterior projection and posterior indentation of the esophagus in the lateral or left anterior oblique projection are characteristic[5,13,15,46,89] (Fig. 82–13). Anomalous right subclavian artery may be recognized with two-dimensional echocardiography when, scanning from the suprasternal notch, the first branch of the aorta is to the right but the normal bifurcation into a right carotid artery and right subclavian artery cannot be demonstrated[87] (Fig. 82–16). Aortic angiography is indicated only in the unusual case requiring surgery. However, the presence or absence of an anomalous right subclavian artery should be noted when aortography is performed in patients with cyanotic congenital heart disease or with coarctation of the aorta (Fig. 82–22).

If symptoms of a vascular ring, such as stridor, wheezing, or cough, are present in a patient with an anomalous right subclavian artery, then consideration should be given to an alternative diagnosis such as laryngotracheomalacia. In rare instances, an anomalous right subclavian artery in association with a left aortic arch, retroesophageal descending aorta, and right ductus arteriosus or ligamentum produces a symptomatic vascular ring.[24,26,27] The retroesophageal descending aorta in these patients produces a large, rounded posterior indentation on a barium esophogram that is usually easily distinguished from the more shallow indentation produced by an anomalous right subclavian artery without a retroesophageal descending aorta. Angiography and surgery should be performed if significant symptoms are present.

The modern surgical approach to symptomatic anomalous right subclavian artery has been described[10,11] and should include division of the anomalous right subclavian artery, dissection of any other retroesophageal component that may be present, and reanastomosis of the anomalous vessel primarily or with prosthetic material. Establishing flow in the right subclavian artery is important to prevent ischemia to the right arm and also to prevent symptoms of cerebral ischemia secondary to the subclavian steal syndrome.[100–102] The surgical approach to patients with vascular ring due to a left aortic arch, retroesophageal descending aorta, anomalous right subclavian artery, and right ductus arteriosus or ligamentum requires a right thoracotomy to facilitate division of the ductus arteriosus or ligamentum and dissection of the retroesophageal component of the descending aorta.[24]

Double Aortic Arch

Double aortic arch is the most common clinically recognized form of vascular ring.[5,15,61,103–107] The ascending aorta divides anterior to the trachea into left and right arches passing to either side of the trachea. Usually, the right arch is larger than the left and passes posterior to the esophagus to join the descending aorta to the left of the midline.[1,22,23] Uncommonly, the left arch may be atretic betweeen the left subclavian artery and the descending aorta, between the left subclavian and the ductus arteriosus, or between the left subclavian and the left carotid artery. Rarely, there may be segmental atresia of the right arch.[24] However, the left arch may be larger and may course posterior to the esophagus and join the descending aorta on the right. A complete vascular ring is formed by the arches on each side of the trachea and esophagus with the ascending aorta anterior and the retroesophageal arch or descending aorta posterior. The ductus arteriosus is usually left sided and is not an essential component of the vascular ring. However, the length of the ductus or ligamentum may significantly affect the severity of symptoms encountered in individual patients. Double aortic arch presumably results from failure of regression of the eighth dorsal aortic arch segment on the right.[5]

Associated congenital heart disease is uncommon.[1,5,23] When

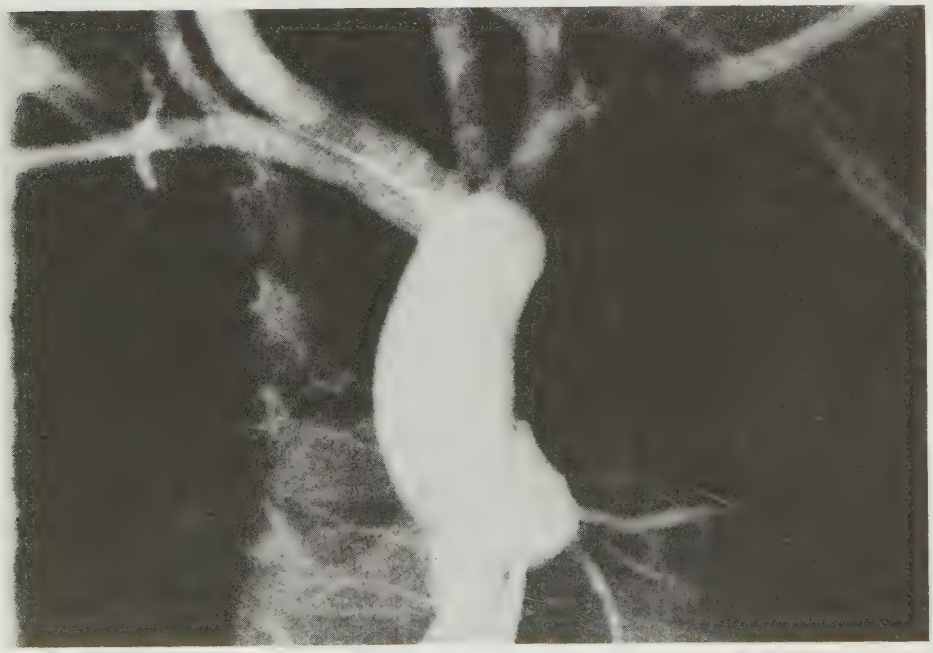

Fig. 82–22. Aortogram of a patient with anomalous origin of the right subclavian artery and tetralogy of Fallot. The right carotid artery arises as the first branch of the aorta but does not divide in the usual fashion. The right subclavian artery arises from the descending aorta as the last brachiocephalic branch.

present, the associated cardiac defects are usually cyanotic and include tetralogy of Fallot[1,23] and transposition of the great arteries.[48] In addition, coarctation may occur in an otherwise patent segment of either arch.[1,5,15]

Patients with double aortic arch are severely symptomatic in infancy with stridor, dyspnea, cough, and recurrent respiratory infections. Infants feed poorly because of severe respiratory distress and may prefer to lie with the head in an extended position. Life-threatening episodes of "reflex apnea" with cyanosis may occur.[62,105] The diagnosis of double aortic arch is often suggested on routine chest radiography.[5,15,46,89] Both arches may be seen to either side of the trachea in the anteroposterior projection, but a right aortic arch with left descending aorta is more commonly seen. This is because most patients with double aortic arch have a dominant right arch with a left descending aorta. There may also be evidence of hyperinflation of either or both lungs caused by obstruction of the lower trachea or tracheal narrowing because of tracheal and esophageal constriction (Fig. 82–12).

Barium esophagography will demonstrate bilateral indentations of the esophagus in the anteroposterior projection.[5,15,46,89] A large oblique defect may be produced by the retroesophageal arch (Fig. 82–14). In the lateral or left anterior oblique projection, a deep posterior indentation is seen and represents the retroesophageal component of the arch. There may also be an anterior more inferior indentation of the arch produced by posterior deviation of the trachea.[89] Characteristic findings of bilateral echolucencies of the double arch will be demonstrated by suprasternal notch echocardiography in the coronal plane[90,91,93] (Fig. 82–20). In addition, it is usually possible to determine the side of the dominant aortic arch and the side of the descending aorta. However, it is not possible to distinguish between right aortic arch with anomalous left subclavian artery and double aortic arch with atresia between the left carotid artery and the left subclavian artery using echocardiography alone.

In double aortic arch, angiography of the ascending aorta will demonstrate both arches, establish the dominant aortic arch, and often differentiate between right aortic arch with anomalous left subclavian artery and double aortic arch with segmental atresia of the left arch[15,21] (Fig. 82–23). As was noted above, angiography with left and right anterior oblique angulation is superior to anteroposterior and lateral projections for demonstration of each arch and the pattern of arterial branching. With patency of both arches, the ascending aorta bifurcates anterior and cephalad to the carina, and each arch courses posteriorly. Usually, the right arch is the larger of the two and can be seen to take a retroesophageal course and join with the left arch to the left of midline to form the descending aorta. The right and left common carotid arteries and subclavian arteries arise separately from each arch. When segmental atresia of the left arch is present, the branching pattern depends on the site of atresia. When atresia occurs between the left subclavian and the left carotid, the branching pattern of the left arch is similar to the branching pattern observed in right aortic arch with anomalous left subclavian artery. The left arch appears to terminate in the left carotid artery, and the left subclavian artery arises from the descending aorta. Usually, traction of the left carotid artery produces a deformity that offers a clue to the presence of the atretic segment and thus aids in the differentiation of this anomaly from right aortic arch with anomalous left subclavian. However, there may be no indication of an atretic segment, making the distinction between these two aortic arch anomalies difficult prior to surgery. Atresia may occur between the left subclavian artery and the ligamentum arteriosus or the ductus arteriosus, in which case the left arch terminates in what appears to be a left innominate artery with a large retroesophageal diverticulum to the left. Again, traction on the base of the left subclavian artery or constriction of the base of the left subclavian artery may suggest the presence of a double aortic arch with segmental atresia of the left arch.

Although some authors advocate a left thoracotomy in all cases, the surgical approach should be determined by the side of the dominant arch.[78,103–111] Since the right arch is dominant in most cases, a left thoracotomy, for division of the smaller or atretic left arch, is employed in most patients. When both arches are of equal size, the approach may be through a left or right thoracotomy, although Kirklin and associates advocate the latter.[78] The essential elements of surgery for double aortic arch include (1) division of the minor arch distal to the origin of the carotid or subclavian artery, (2) ligation and division of the ductus arteriosus or ligamentum arteriosus, and (3) complete dissection and mobilization of remaining components of the divided arch with dissection and division of any adventitial bands that form a part of the constricting mechanism.[6,78,103–108] Mortality is low, and eventual long-term relief of symptoms is usually achieved. However, short-term residual tracheal obstruction is the rule,[78] and most infants require intubation and aggressive attention to pulmonary toilet in the early postoperative period. Tracheomalacia may also coexist, leading to a need for long-term intubation or trachostomy.

Right Aortic Arch, Anomalous Left Subclavian Artery, and Left Ductus Arteriosus

Right aortic arch with anomalous left subclavian artery and left ductus arteriosus is the most common type of aortic arch anomaly that produces an anatomic vascular ring.[15] However, this group of abnormalities is usually asymptomatic[15,50] and therefore ranks as the second most common cause of symptomatic vascular ring requiring surgery.[103–107] The essential pathologic features include course of the arch to the right of the trachea with the first branch being the left carotid artery. The left subclavian artery arises from the descending aorta, and the ductus arteriosus originates from a retroesophageal diverticulum of the descending aorta and courses to the left to connect to the pulmonary artery. The descending aorta may take a retroesophageal course high in the thorax and descend on the left. In contrast to double aortic arch, the presence of a left ductus arteriosus is an essential component of the vascular ring. When the left ductus or ligamentum is absent, no vascular ring is formed.

Associated congenital heart disease is uncommon, occurring in less than 5% of patients with this group of abnormalities.[15,50] This is in contrast to right aortic arch with mirror-image branching in which cyanotic congenital heart disease is almost always present.[1,49–52]

As was noted above, patients with right aortic arch, anomalous left subclavian artery, and left ductus arteriosus are usually asymptomatic. When symptoms of tracheal or esophageal obstruction occur, they are similar to those encountered in patients with double aortic arch but are milder and often lead to presentation later in life.[106] Nonetheless, when symptomatic, patients will present with stridor, cough, and recurrent respiratory infections. Older patients

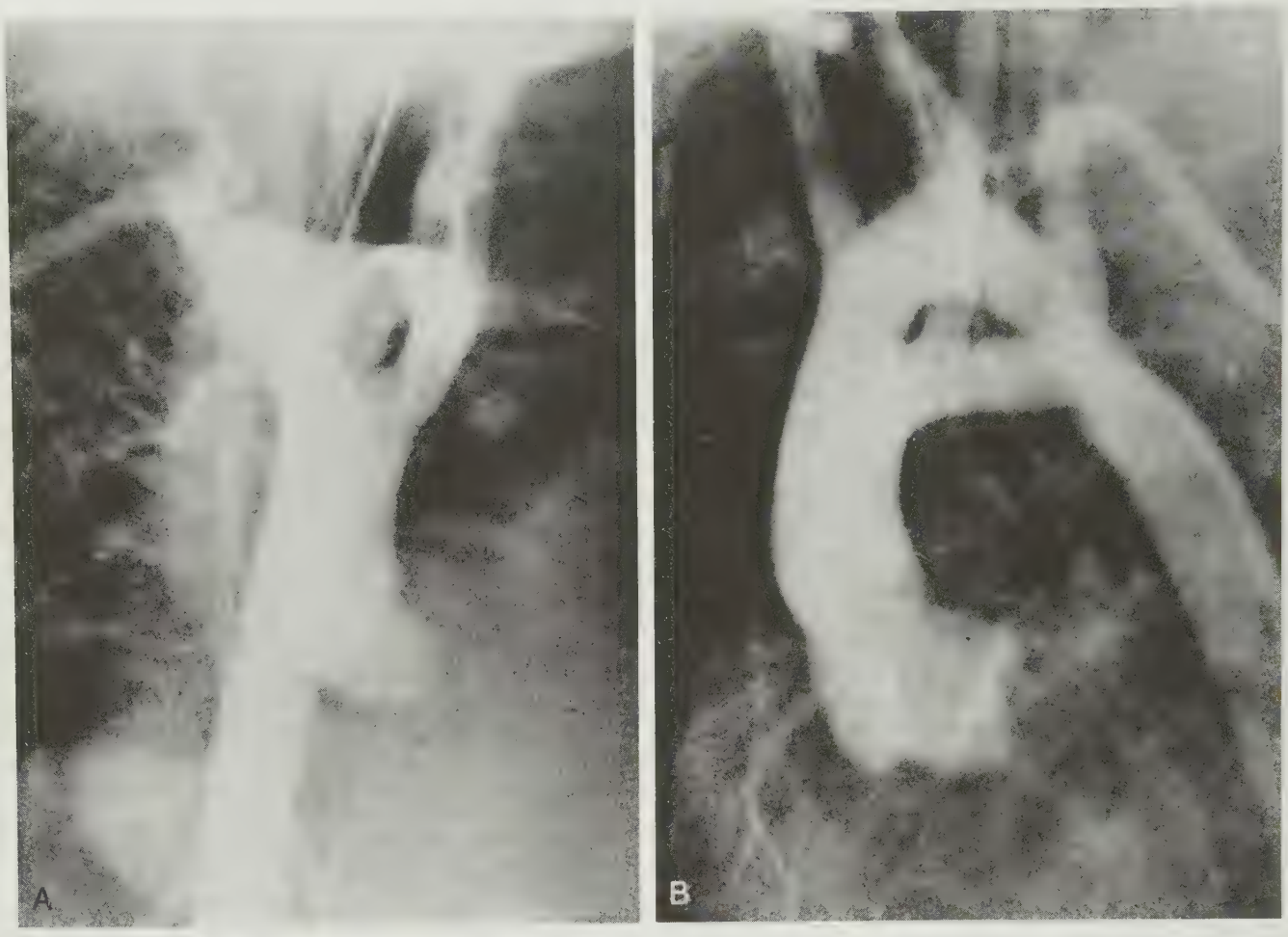

Fig. 82–23. Cranial (A) and left anterior oblique (B) cineangiograms in a patient with double aortic arch. The position of the trachea is demonstrated by the presence of the endotracheal tube. The ascending aorta divides to form the right aortic arch and left aortic arch. Both arches are patent, and separate origin of the carotid and subclavian arteries from each arch is demonstrated. In both views, the right aortic arch appears to be the larger of the two.

may complain of dysphagia and may not have a history of stridor or wheezing. Anteroposterior chest radiographs demonstrate deviation of the trachea to the left produced by the density of the right aortic arch (Fig. 82–11). The descending aorta may be on the left or the right. Barium esophagography demonstrates an oblique indentation from right to left (Fig. 82–15) in the anteroposterior projection and a posterior indentation of the esophagus in lateral and left anterior oblique views.[15,46,89] The size of the posterior indentation depends on the size of the retroesophageal component of the arch. A small indentation is produced by an anomalous left subclavian, whereas a larger indentation will be produced by a retroesophageal diverticulum or a retroesophageal descending aorta. On suprasternal notch echocardiography, the presence of a right aortic arch with anomalous left subclavian artery is confirmed by demonstrating the left carotid artery as the first branch of the arch[90] (Fig. 82–18). In sagittal views, the descending aorta is seen to course to the right of the trachea and descend on the right. A retroesophageal diverticulum can be demonstrated by scanning from right to left in a sagittal plane. When patent, the ductus arteriosus can be seen arising from the retroesophageal diverticulum and connecting to the pulmonary artery. Patency of the ductus arteriosus is confirmed by pulsed Doppler sampling in the pulmonary artery (Fig. 82–19). Thus echocardiographic demonstration of a right aortic arch with the first branch of the ascending aorta to the left without bifurcation strongly suggests the possibility of a vascular ring.

Angiography is reserved for patients in whom surgery is being contemplated. The first branch of the arch to opacify will be the left carotid artery, followed by the right carotid and subclavian arteries (Fig. 82–24). The arch courses to the right of the trachea as branching occurs; it then usually pursues a retroesophageal course, and the left subclavian artery arises from a diverticulum of the descending aorta. The ductus arteriosus opacifies when patent.

Stenosis of the anomalous left subclavian artery may be seen as it arises from the retroesophageal diverticulum and is probably produced by constriction of the ductus arteriosus at its origin at the bases of the left subclavian artery.[15,21] The origin of the left subclavian artery may be atretic, and therefore the left subclavian artery may be "isolated" from continuity with the aorta.[5,15] An isolated left subclavian then opacifies through the left vertebral artery by way of collaterals. The ductus arteriosus connects to a retroesophageal diverticulum when the left subclavian artery is anomalous. However, isolation of the left subclavian artery is more

Fig. 82–24. Retrograde aortic cineangiogram in the anteroposterior projection in a patient with right aortic arch and anomalous left subclavian artery. The left carotid artery arises as the first branch of the aorta, and the arch courses to the right of the trachea. The left subclavian artery originates from a retroesophageal Kommerell's diverticulum. The constriction at the base of the left subclavian artery (arrow) is probably produced by ductal constriction and indicates the presence of a left ductus arteriosus and a vascular ring.

often associated with right aortic arch with mirror-image branching where the isolated subclavian artery presumably results from atresia of the arch between the left carotid and subclavian arteries. In these patients, the ductus arteriosus connects to the base of the left subclavian artery as it does in most patients with right aortic arch and mirror-image branching.[5,15] This defect is commonly associated with tetralogy of Fallot[5,12,15,101] or other congenital cardiac defects. The essential difference between patients with isolation of the left subclavian artery and right aortic arch with mirror-image branching and those without mirror-image branching is the presence of a retroesophageal diverticulum in the latter group.

Surgery is indicated in patients who are symptomatic from significant tracheal or esophageal compression. The surgical approach includes ligation and division of the left ductus arteriosus or ligamentum, division of the left subclavian and reimplantation, and dissection of all retroesophageal components with division of all constricting bands.[78,103–107,109] As in the case of double aortic arch, surgical mortality is low, and long-term relief of symptoms is the rule.

Cervical Aortic Arch

Cervical aortic arch is an uncommon anomaly that may be described by three essential features.[28] First, there is cervical position of the aorta. The apex of the arch is above the clavicle and usually at the level of the fifth through the seventh cervical vertebrae.[1] Second, there is separate origin of the carotid artery contralateral to the arch. In addition, there is usually separate origin of the internal carotid, external carotid, and subclavian arteries on the side of the arch. Third, the descending aorta enters the thorax from the neck on the side of the arch, then crosses posterior to the esophagus in the upper thorax to descend and exit the thorax. There may be a ductus arteriosus or ligamentum originating from the descending aorta on the side contralateral to the arch. This in turn produces a vascular ring. Associated congenital heart disease is uncommon.[1,28,68] Cervical aortic arch may result from persistence of the embryonic right or left third dorsal aortic arch or from failure of the arch to descend into the thorax during development and growth of the embryo.[1,15,28,29]

Although many patients with cervical aortic arch are asymptomatic, when symptoms are present they may range from dysphagia to significant respiratory distress. The latter occurs when there is a coexisting vascular ring. There is always a pulsatile mass noted in the neck.[28] Compression of the mass produces a palpable reduction in leg pulses as well as the arm pulse on the side opposite the aortic arch. This physical finding is pathognomonic for cervical aortic arch. In addition, a thrill and murmur are present over the mass, and there may be other findings compatible with congenital heart disease on examination.

Routine chest radiography will demonstrate loss of the normal aortic knob on the left, widening of the superior mediastinum,[15] and an aortic density in the apex of the hemithorax on the side of the arch. There is a large posterior indentation of the esophagus in the lateral projection on esophagography.[15] Although cervical arch has been recognized by using two-dimensional echocardiography, the variations in arterial branching pattern that may be present make angiography a prerequisite to surgical repair. In a typical case, aortography reveals an elongated ascending aorta and the apex of the aortic arch above the clavicle (Fig. 82–25). Most often, the aortic arch is on the right. The aorta then turns caudally and reenters the thorax. The branching pattern of the brachiocephalic vessels is variable. The first branch is usually the left common carotid followed by the right internal carotid, the right external carotid, and the right subclavian artery. The left subclavian artery arises from the descending aorta after the descending aorta crosses the midline to the left. Rarely, with cervical position of the aortic arch, the arch and the descending aorta may be on the left, in which case a normal arterial branching pattern is observed. When the aortic arch and the descending aorta are on the right, the first branch of the aorta is a left common carotid artery with an anomalous left subclavian artery arising from the descending aorta.

Surgery is reserved for patients with symptoms of tracheal or esophageal compression or for patients with aneurysm formation or coarctation. The surgical approach to patients with cervical aortic arch has been described by Cooley.[111]

Fig. 82–25. Anteroposterior cineangiogram in an unusual patient with cervical aortic arch. The aortic arch ascends to the right with the apex above the right clavicle, then descends into the thorax to pursue a retroesophageal course to the left. The order of branching of the brachiocephalic vessels is left brachiocephalic artery, right internal carotid artery, right external carotid artery, and right subclavian artery. Typically, in contrast to this example, the subclavian artery on the side opposite the arch usually arises as the last branch of the aorta.

Anomalous Innominate Artery

Patients with stridor and respiratory distress in infancy associated with anterior compression of the trachea have been described with symptoms attributed to compression of the trachea by an anomalous origin and course of the innominate artery.[57–62] A number of investigators have advocated surgical intervention in patients with stridor and "reflex apnea" who manifest anterior tracheal compression on lateral chest radiographs and at bronchoscopy. Others have disputed the role of the innominate artery in producing symptoms and have cited the high incidence of tracheomalacia in affected infants and the frequent finding of anterior tracheal indentation in asymptomatic children.[63–67] It is clear that the innominate artery may arise more distal on the aortic arch and produce a striking degree of tracheal indentation in its course across the anterior mediastinum. However, Swischuk[63] and Berdon and associates[89] have emphasized the role of anterior mediastinal crowding, which is demonstrable on lateral chest radiographs in normal infants, in producing apparent anterior tracheal compression. In addition, varying degrees of anterior tracheal compression by the innominate artery may be seen at bronchoscopy in asymptomatic children.[67] This finding is seen in both asymptomatic and symptomatic infants and apparently resolves with age.

Symptoms ascribed to innominate artery compression are basically the same as those caused by tracheomalacia. Affected infants have cough, stridor, and dyspnea and may have episodes of apnea and cyanosis. Infants who experience apnea and cyanosis have a serious prognosis. In addition to the findings on chest radiographs and bronchoscopy noted above, echocardiography will demonstrate a normal left aortic arch with the first branch being the innominate artery to the right. Barium esophagography is normal, excluding vascular rings and vascular slings. In infants experiencing apnea, the diagnosis of more common causes of apnea should be vigorously pursued.

Most affected infants improve without surgical intervention. It is interesting that the contemporary surgical approach for symptomatic tracheomalacia is essentially the same as the procedure advocated for symptomatic anomalous innominate artery.[64] The indication for surgery in both conditions is the severity of symptoms. The innominate artery, the aorta, and the anterior mediastinal fascia are sutured to the posterior sternal periosteum in an attempt to relieve compression. Some authors have reported good relief of symptoms and have concluded that the innominate artery must have been the cause of stridor and respiratory distress.[57–62] However, similar results are obtained in severely symptomatic patients with tracheomalacia who do not have distal origin of the innominate artery or striking discrete tracheal compression. It is likely that the primary diagnosis in the majority of patients is localized or diffuse tracheomalacia and that the effect of surgery is to reduce the extrinsic compression produced by "anterior mediastinal crowding."[63]

Anomalous Left Pulmonary Artery

Anomalous origin of the left pulmonary artery is a rare congenital anomaly that produces severe tracheobronchial obstruction in most affected patients. A normal left pulmonary artery is absent, and the left lung is supplied wholly or partially by an anomalous left pulmonary artery arising from the distal right pulmonary artery. Tracheal and bronchial compression is produced as this artery courses posterior and caudal to the right main stem bronchus and to the left, posterior to the trachea and anterior to the esophagus. The vessel then proceeds to the left hilum posterior to the left bronchus and enters the lung. The course of the vessel to the right of the trachea produces deviation of the lower trachea to the left. The resulting compression of the right main stem bronchus and lower trachea leads to airway obstruction primarily affecting the right lung. However, compression of the lower trachea and left main stem bronchus may occur, resulting in bilateral obstruction.

The anomalous left pulmonary artery is usually the sole arterial supply to the left lung. However, arterial supply to the left lower lobe by the anomalous left pulmonary artery with arterial supply to the left upper lobe by a left pulmonary artery in the normal position has been described.[34] In addition, partial arterial supply to the right upper lobe by an arterial branch originating from the anomalous left pulmonary artery has also been described.[71] The frequent occurrence of associated congenital defects, particularly those affecting the lung, is described above.

Symptoms of anomalous left pulmonary artery occur early in the great majority of patients. Although two thirds of affected infants are symptomatic by one month of age,[36] the diagnosis is made in only 14% of these patients. In some cases, the anomaly is not recognized until postmortem examination. Symptoms include severe respiratory distress with stridor, wheezing, cyanosis, and recurrent pneumonitis. Obstructive apnea may occur and can be fatal. Unlike aortic vascular rings, dysphagia is rare, since the anomalous left pulmonary artery passes anterior to the esophagus without significant esophageal compression. Although the majority of patients are severely symptomatic, asymptomatic and mildly affected patients have been observed.[77,112] Nonetheless, in severely affected infants, death may occur within the first six months of life unless surgery is performed.[70]

On anteroposterior chest radiographs, the lower trachea is deviated to the left and may appear "squeezed together."[1] Hyperinflation of the right lung is commonly observed because of compression of the right main stem bronchus. The degree of hyperinflation may be severe and may lead to a mistaken diagnosis of congenital lobar emphysema. Left-sided hyperinflation may also be seen on chest radiographs because of obstruction of the carina or left bronchus. Atelectasis of a single lobe or lung is observed in patients with severe obstruction. A mediastinal mass may be seen posterior to the trachea and anterior to the esophagus at the level of the carina.[36]

Barium esophagography usually demonstrates a characteristic anterior indentation of the esophagus on the lateral projection[15,76,89] (Fig. 82–26). The esophagus may be displaced to the right in the frontal projection and demonstrates an oblique impression immediately posterior to the carina. Demonstration of characteristic echocardiographic findings in affected patients may obviate the need for esophagography. Scanning in a coronal plane from the suprasternal notch (Fig. 82–21) and from the parasternal short axis demonstrates absence of the normal bifurcation of the main pulmonary artery into right and left pulmonary arteries. The left pulmonary artery appears to be absent. Examination of the right pulmonary artery will reveal a vessel arising from the posterior surface of the right pulmonary artery that can be followed posterior to the trachea and anterior to the esophagus. The vessel then passes anterior to the descending aorta and enters the left hilum. Yeager and associates[95] have described imaging of the anomalous left pulmonary artery from the subxiphoid position in five patients with anomalous left pulmonary artery with successful identification of the anomaly in four. The same principles of diagnosis apply to the subxiphoid view with demonstration of absence of a normal left pulmonary artery and origin of the anomalous left pulmonary artery from the posterior surface of the right pulmonary artery. However, the course of the left pulmonary artery with respect to the trachea and esophagus may be more difficult to image from the subxiphoid position. In addition to demonstration of the anomalous left pulmonary artery, two-dimensional echocardiography accurately diagnoses and describes associated cardiac defects.

Although the presence of a "vascular sling" can be established noninvasively, pulmonary artery angiography remains necessary to delineate the anatomic detail necessary for surgical correction. Mixed arterial supply to the right or left lung by the anomalous left pulmonary artery will necessitate alterations in surgical technique and cannot be completely described by using noninvasive

Fig. 82–26. Barium esophagogram in a patient with anomalous left pulmonary artery. In the anteroposterior projection (left panel), the trachea is deviated to the left, and there is compression of the esophagus on the left. In the lateral projection (right panel), the characteristic anterior indentation of the esophagus just above the carina can be seen. (From Gumbiner, C.H., Mullins, C.E., and McNamara, D.G.: Pulmonary artery sling. Am. J. Cardiol., *45*:311, 1980.)

techniques alone. A vascular sling produced by an anomalous ductus arteriosus[8,113] could be mistaken for an anomalous left pulmonary artery by esophagography. However, both of these unusual situations, with exception of partial supply to the right lung by the anomalous left pulmonary artery, should be suspected on two-dimensional echocardiography if the criteria described above for the diagnosis of anomalous left pulmonary artery are strictly observed.

On angiography, the origin and course of the anomalous left pulmonary artery are best demonstrated by contrast injection into the main pulmonary artery using a steep cranial angulation of 60 to 70% or by using the sitting-up view[21,77,112] (Fig. 82–27). In the anteroposterior projection, absence of a normal left pulmonary artery can be seen, but the origin of the anomalous left pulmonary is partially obscured by the right pulmonary artery. Catheterization is also indicated to assess the severity of associated cardiac defects.

Survival of symptomatic infants is unlikely without early surgical intervention. Therefore surgery should be performed early in infants suffering from severe respiratory obstruction. Planning the surgical approach for these patients is often complicated by the presence of associated congenital heart disease as well as pulmonary anomalies. Patients who are free of respiratory obstruction or are mildly affected do not require surgical correction of the anomalous left pulmonary artery. However, surgery for repair of associated cardiac defects may be necessary. Potts[114] described the first surgical procedure for correction of anomalous

Fig. 82–27. Anteroposterior (A) and cranial (B) cineangiograms in a patient with anomalous left pulmonary artery. In the anteroposterior right ventricular cineangiogram (A), the absence of a normal left pulmonary artery can be seen as well as the origin of the left pulmonary artery from the right pulmonary artery. However, both the origin of the left pulmonary artery and its course posterior to the trachea are seen to better advantage with main pulmonary artery cineangiography with steep cranial angulation (B). (Part B is from Gumbiner, C.H., Mullins, C.E., and McNamara, D.G.: Pulmonary artery sling. Am. J. Cardiol., *45*:311, 1980.)

left pulmonary artery in 1954. Although there have been many subsequent reports describing successful treatment of this anomaly by surgery,[36,76,78,103–105,115,116] mortality remains high. Sade and associates,[36] Koopot and associates,[76] and Kirklin and associates[78] have reviewed the surgical experience with anomalous left pulmonary artery. The major approach to this lesion involves division of the anomalous vessel and reanastomosis to the main pulmonary artery anterior to the trachea. This may be accomplished through either a left posterolateral thoracotomy or median sternotomy with cardiopulmonary bypass.[36,76,78] Surgical and postoperative mortality is approximately 40 to 50%. Coexisting tracheal or bronchial stenosis is disproportionately prevalent and severe in nonsurvivors and is undoubtedly a major contributing factor to postoperative death. This has led some authors to recommend bronchographic or bronchoscopic[77] evaluation of selected surgical candidates, since surgical reconstruction of obstructed bronchi may be required. In addition, careful attention to tracheobronchial toilet in the postoperative period is necessary to avoid airway obstruction caused by secretions. Despite a high incidence of postoperative stenosis of the left pulmonary artery, surgical survivors are often free of significant symptoms at long-term followup.[36,78] However, some degree of airway obstruction may persist in up to 45% of patients who survive surgery.[117]

Unilateral Absence of One Pulmonary Artery

Unilateral absence of one pulmonary artery is an uncommon congenital defect. Forty percent of cases occur without associated cardiac defects, whereas the remaining patients have tetralogy of Fallot, patent ductus arteriosus, or ventricular septal defect.[31] The absent pulmonary artery is usually opposite the side of the aortic arch. When associated with tetralogy of Fallot, the absent pulmonary artery is usually on the left. In addition, patients with atrial septal defects, aortopulmonary window, subaortic stenosis with coarctation, transposition, aberrant left subclavian artery, and truncus arteriosus have been reported.[31–33] The distal pulmonary artery on the affected side can often be identified at surgery; thus the term "occult pulmonary artery" as suggested by Presbitero and associates[32] may be more appropriate.

Patients without associated cardiac defects are often asymptomatic but may experience recurrent pneumonitis, bronchiectasis, or hemoptysis. When associated congenital heart disease is present, symptoms are generally those of the associated defect. Patients with left-to-right shunts may experience severe symptoms of pulmonary congestion, since both the normal cardiac output and the left-to-right shunt must perfuse the normally connected pulmonary artery. Likewise, there are no specific physical findings that indicate unilateral absence of a pulmonary artery. Most patients have a systolic murmur at the left sternal border. Those with coexisting cardiac defects have compatible physical findings.

Differential perfusion of the lungs with reduced vascular markings may not be apparent in infants in chest radiographs. However, in older children and adults, increased vascular markings on the side with normal pulmonary artery connection and decreased markings on the affected side may be seen.

Absence of a pulmonary artery will be readily apparent by two-dimensional echocardiography, particularly in short-axis and suprasternal notch scans in which the normal bifurcation of the main pulmonary artery is absent. However, a careful search should be made for connection of the involved pulmonary artery to the ascending aorta or, in the case of anomalous left pulmonary artery, to the right pulmonary artery.[84,90] Identification of ductal supply to the occult pulmonary artery should be possible in neonates using combined high-frequency (7.5 or 10 mHz) mechanical scanning and pulsed Doppler. In addition, associated cardiac defects will be identified by two-dimensional echocardiography as well as the side of the aortic arch. Perfusion lung scan, in the absence of right-to-left cardiac shunts, demonstrates perfusion of only the normally connected lung. Right ventricular or pulmonary artery angiography will demonstrate the absent pulmonary artery and the normally connected pulmonary artery (Fig. 82–28). Aortography is useful in identifying the source of systemic arterial supply to the affected lung. Cardiac catheterization also allows accurate assessment of pulmonary artery pressure and resistance in the normally connected lung. Approximately 20% of patients without associated left-to-right shunts will demonstrate evidence of pulmonary hypertension, whereas 88% of those with left-to-right shunts have pulmonary hypertension.[31] Although pulmonary hypertension is not present in patients with tetralogy of Fallot, catheterization following repair of this defect may demonstrate elevated pulmonary resistance.[31]

In patients with isolated unilateral absence of one pulmonary artery, treatment depends on the severity of symptoms. Pneumonitis may be treated medically, but if severe recurrent lung infections or hemoptysis occurs, consideration should be given to pneumonectomy of the affected lung. The presence of pulmonary vascular disease in the unaffected lung would preclude pneumonectomy. Early surgical identification of the occult pulmonary artery may allow establishment of arterial supply and maintenance of growth of the true pulmonary artery, thus discouraging collateralization.[32] However, in the absence of associated congenital heart disease, many of these infants will be asymptomatic and therefore escape recognition.

Patients with coexisting left-to-right shunts should undergo early surgical repair of the intracardiac or extracardiac shunt to prevent development of irreversible pulmonary hypertension.[31] Surgery should be performed in the first three to six months of life, although pulmonary hypertension may progress despite surgical intervention.

Origin of One Pulmonary Artery from the Ascending Aorta

As was noted above, origin of one pulmonary artery from the ascending aorta is a rare anomaly, occurring in 0.05% of patients with congenital heart disease.[80] In most patients, the right pulmonary artery arises from the ascending aorta and is usually the same size as, or larger than, the left pulmonary artery. The vessel connects to the aorta just above the aortic valve and on the right or posterior and courses directly to the right hilum. Most patients with origin of one pulmonary artery from the ascending aorta have a patent ductus arteriosus.[80–82] Cardiac defects associated with origin of the right pulmonary artery from the ascending aorta include ventricular septal defect, aortopulmonary window, coarctation of the aorta, interrupted aortic arch, atrial septal defect, and contralateral pulmonary vein stenosis.[78,80]

In some patients, the left pulmonary artery originates from the ascending aorta. This occurs as an isolated anomaly in approximately 40% of cases. In these patients, the aortic arch is usually on the right. In the remaining patients with origin of the left pulmonary artery from the ascending aorta, tetralogy of Fallot is

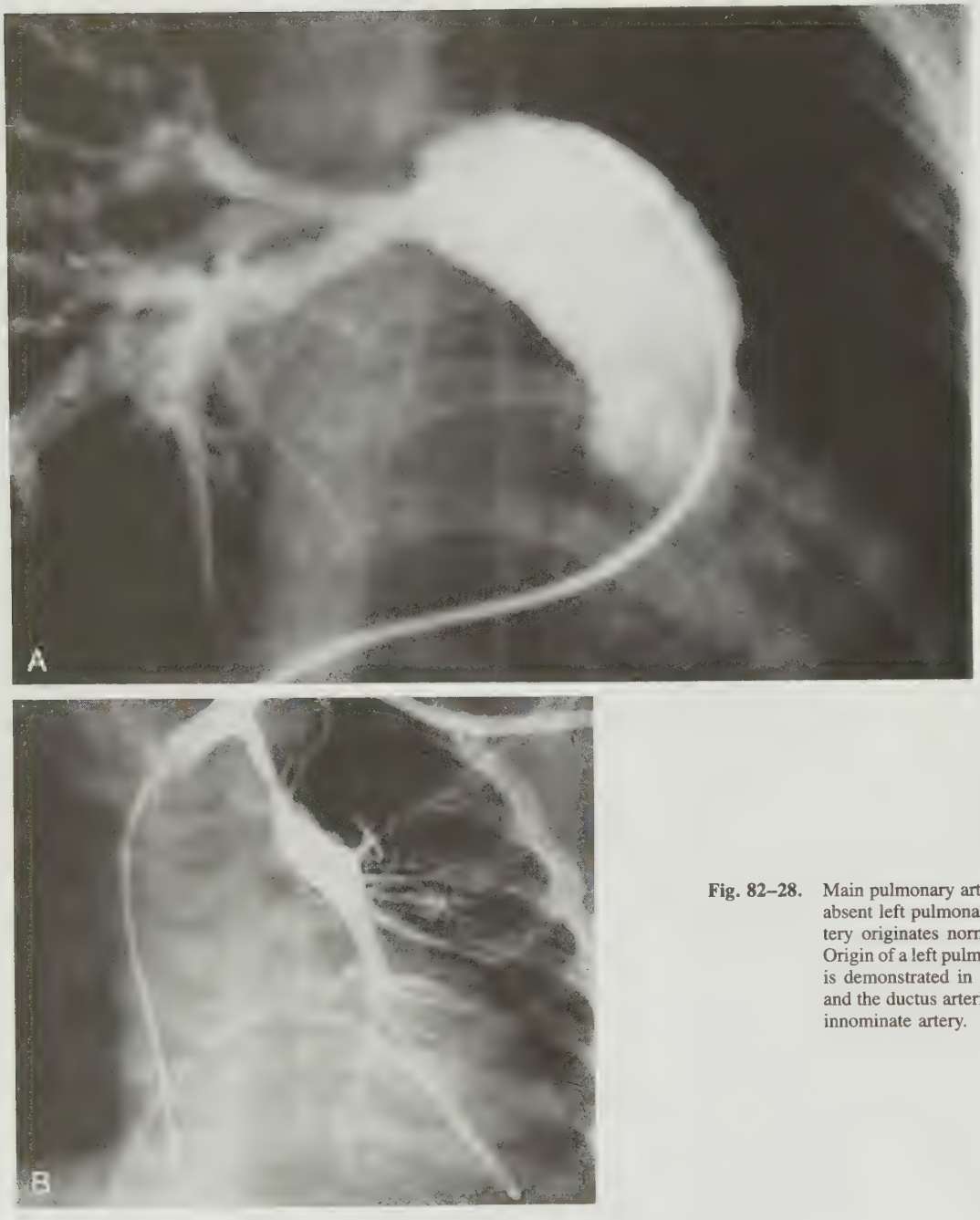

Fig. 82–28. Main pulmonary artery cineangiogram (A) in a patient with absent left pulmonary. The hypoplastic right pulmonary artery originates normally from the main pulmonary artery. Origin of a left pulmonary artery from a left ductus arteriosus is demonstrated in part B. The aortic arch is to the right, and the ductus arteriosus originates from the base of the left innominate artery.

often present.[81,84] In addition, tetralogy of Fallot may also occur in patients with anomalous origin of the right pulmonary artery.[78,80,84] The embryopathogenesis of anomalous origin of one pulmonary artery from the ascending aorta is discussed above.

Patients with origin of one pulmonary artery from the ascending aorta characteristically present in early infancy with severe congestive heart failure. Affected infants often manifest cyanosis in the absence of cyanotic congenital heart disease.[80] In these patients, cyanosis results from a right-to-left shunt at the ductal level caused by pulmonary hypertension.[33,80] The heart is often massively enlarged on chest radiographs, and the pulmonary vascular markings either are symmetrically increased or are greater on the affected side. The diagnosis may be made by two-dimensional echocardiography[84,90,95,97] (Fig. 82–29). The origin of the anomalous pulmonary artery from the aorta, usually on the right, can be demonstrated in the short-axis and suprasternal notch scans and may be distinguished from aortopulmonary window by demonstrating lack of continuity of the right and left pulmonary arteries.[97] The presence of a ductal shunt, which is usually bidirectional, can be established by pulsed Doppler interrogation of the ductus arteriosus and main pulmonary artery. Echocardiographic examination will demonstrate two arterial valves except in some patients with severe pulmonary atresia associated with extreme hypoplasia or absence of the main pulmonary artery.[84] In these patients, the differentiation from truncus arteriosus may be aided by demonstrating a blind right ventricular outflow tract and three aortic valve cusps. In addition, echocardiography will clearly delineate other associated cardiac defects. Catheterization is useful in determining the pulmonary artery resistance in the normally connected lung. Aortography will demonstrate the anomalous vessel, and ventricular cineangiography will identify associated cardiac defects (Fig. 82–30).

Although significant pulmonary vascular obstructive disease is not present in infants who die before six months of age, obstructive changes may be present soon thereafter.[80] Without surgical intervention, most patients will die by six months of age.[78] Pulmonary hypertension is present on the affected side in all patients except the rare patient with stenosis of the origin of the anomalous vessel.[34,80] Arterial pressure in the normally connected pulmonary artery is usually at systemic levels except in patients with tetralogy of Fallot. Thus early surgical repair is indicated when the diagnosis of unilateral origin of a pulmonary artery from the ascending aorta is established. Accurate assessment of pulmonary resistance in the normally connected lung is important in patients presenting after six months of age. Significant elevation in resistance may be a contraindication to surgery in these patients. Surgical division and anastomosis of the affected artery to the main pulmonary artery are performed through a median sternotomy using cardiopulmo-

Fig. 82–29. Echocardiographic demonstration of origin of the right pulmonary artery from the ascending aorta. In the upper and lower left panels, the right pulmonary artery (RPA) originates from the ascending aorta (Ao) without communication with the left pulmonary artery (LPA). In the upper and lower right panels, the origin of the left pulmonary artery from the main pulmonary artery (MPA) is established. The presence of an aortic valve (AV) and pulmonary valve (PVal) distinguishes this condition from truncus arteriosus. LA = left atrium. (From King, D.L., Huhta, J.C., Gutgesell, H.P., and Ott, D.A.: Two-dimensional echocardiographic diagnosis of anomalous origin of the right pulmonary artery from the aorta: Differentiation from aortopulmonary window. J. Am. Coll. Cardiol., *4*:351, 1984.)

Fig. 82–30. Aortic cineangiography in a patient with origin of the right pulmonary artery from the ascending aorta. The right pulmonary artery arises from the ascending aorta just above the aortic sinuses of Valsalva. The presence of two semilunar valves and normal origin of the left pulmonary artery distinguish this condition from truncus arteriosus. (From King, D.L., Huhta, J.C., Gutgesell, H.P., and Ott, D.A.: Two-dimensional echocardiographic diagnosis of anomalous origin of the right pulmonary artery from the aorta: Differentiation from aortopulmonary window. J. Am. Coll. Cardiol., *4*:351, 1984.)

nary bypass with hypothermia.[78] Surgical results in patients without associated cardiac defects or with patent ductus arteriosus are good,[78,80,82,118] although results in patients with associated cardiac defects other than patent ductus arteriosus are generally poor. Survivors of surgery in infancy usually have normal pulmonary artery pressure and resistance at followup.[80,82,118]

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CHAPTER 83

Congenital Coronary Artery Anomalies

David J Driscoll

CORONARY ARTERY ANOMALIES

As Leonardo da Vinci said, "The heart in itself is not the beginning of life; but it is a vessel formed of thick muscle, vivified and nourished by the artery and vein as are the other muscles."

Normal Coronary Anatomy

The term "coronary" is derived from the Latin "coronarius," or "crown," because the coronary arteries cover the heart in a fashion reminiscent of a crown covering a head. Usually, there are two major coronary arteries, which originate from the right and left aortic sinuses of Valsalva. Commonly, however, branches of the right or left coronary artery have separate origins from the sinuses of Valsalva. The sinuses of Valsalva consist of portions of the aorta between the sinotubular ridge and the aortic valve leaflets. The third, or posterior, sinus of Valsalva is usually slightly larger than the left or right sinus of Valsalva, is unassociated with a coronary artery orifice, and is termed the noncoronary sinus of Valsalva or noncoronary aortic cusp.[1]

The Left Coronary Artery

The left main coronary artery arises from the left sinus of Valsalva and courses only a short distance (less than 4 cm in the adult) before dividing into the left circumflex and left anterior descending coronary arteries (Fig. 83–1). The left circumflex coronary artery varies considerably in size depending upon whether the posterior descending coronary artery is a branch of the right coronary artery ("right-dominant coronary system") or a branch of the circumflex coronary artery ("left-dominant coronary system"). If the posterior descending coronary artery originates from the circumflex coronary artery (this occurs in about 10% of patients), the circumflex coronary artery is large. In some patients with a dominant right coronary artery, the circumflex coronary artery may be quite small. The circumflex coronary artery travels under the left atrial appendage and along the groove of the left atrioventricular valve. In 50% of cases, the sinus node artery arises from the left circumflex coronary artery. The sinus node artery courses under the left atrial appendage, penetrates the interatrial septum, encircles the base of the superior vena cava, and supplies the sinus node. When the sinus node artery is not a branch of the left circumflex coronary artery, it is a branch of the right coronary artery. Kugel's artery may arise from the left circumflex coronary artery (alternatively, it may arise from the right or left main coronary artery) and courses through the interatrial septum anastomosing with the artery to the atrioventricular node. Marginal branches arise from the left circumflex coronary artery and supply areas of the lateral wall of the left ventricle. The largest marginal branch is termed the obtuse marginal. The left atrial circumflex artery may arise from the left circumflex coronary artery and supply the left posterior atrial wall. Occasionally, the sinus node artery can arise from the left atrial circumflex coronary artery.

The left anterior descending coronary artery appears to be a direct continuation of the left main coronary artery rather than a branch of it. The left anterior descending coronary artery travels along the interventricular sulcus and may continue around the apex of the heart onto the posterior interventricular sulcus to anastomose with the posterior descending coronary artery. The left conus artery is the first branch of the left anterior descending coronary artery and may anastomose with the conal branch of the right coronary artery, forming the "circle of Vieussens." Four to six septal

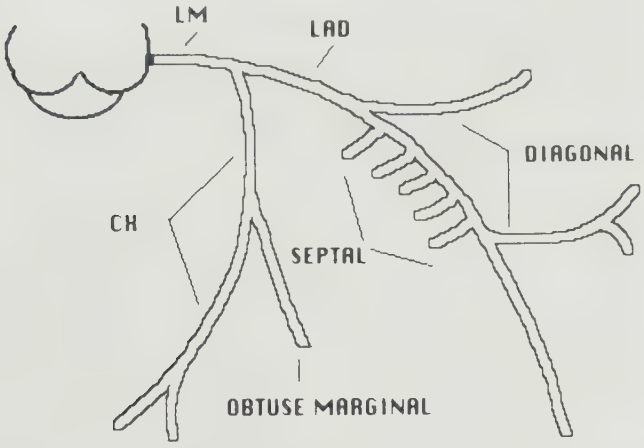

Fig. 83–1. Normal left coronary artery system. CX = circumflex; LM = left main; LAD = left anterior descending coronary arteries.

branches of the left anterior descending coronary artery penetrate the ventricular septum and anastomose with posterior septal branches arising from the posterior descending coronary artery. The left anterior descending coronary artery gives rise to diagonal branches that supply the anterior surface of the right and left ventricles and the right ventricular infundibulum.

The Right Coronary Artery

The right coronary artery arises from the right aortic sinus of Valsalva and courses behind the pulmonary artery beneath the right atrial appendage and along the right atrioventricular groove (Fig. 83–2). At the acute margin of the heart, it turns posteriorly and caudally over the diaphragmatic surface of the heart. The branches of the right coronary artery include the right conal branch, the sinus node artery, an atrial branch, right ventricular muscle branches (including the acute marginal branch), posterior descending coronary artery, atrioventricular node artery, and septal branches. The right conus artery is the first branch of the right

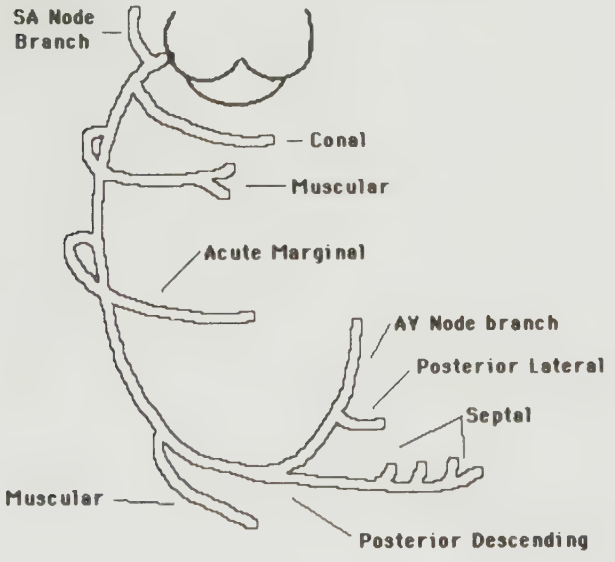

Fig. 83–2. Normal right coronary artery system.

coronary artery in about 50% of cases; in the others, it arises directly from the right aortic sinus of Valsalva. The sinus node artery arises from the right coronary artery in 50% of cases and from the left circumflex artery in the remainder (see above). The right ventricular free wall is supplied by several branches of the right coronary artery. The largest of these branches is the acute marginal branch of the right coronary artery.

As was noted above, 90% of people have a "dominant right coronary artery system." That is, the posterior descending coronary artery is a branch of the right coronary artery. In the remainder, the descending coronary artery originates from the left coronary artery. The term "dominant right coronary artery system" refers only to the origin of the posterior descending coronary artery and not to the coronary artery that supplies most of the myocardium. Indeed, except in unusual circumstances, the majority of the myocardium is supplied by the left coronary artery regardless of the "dominance" of the coronary artery system.

The posterior descending coronary artery supplies the lower portion of the ventricular septum. The septal branches of the posterior descending coronary artery anastomose with the septal branches of the left anterior descending coronary artery. Muscular branches supplying the diaphragmatic portions of the right and left ventricles also arise from the posterior descending coronary artery. The artery to the atrioventricular node originates from the posterior descending coronary artery and travels cephalad to reach the atrioventricular node.

Minor Variations of Normal Coronary Anatomy

Variations in the number of coronary ostia are so frequent that it is difficult to know whether two ostia or three ostia are "normal." In approximately 50% of cases, the right conus artery originates from a separate orifice of the right coronary cusp. A total of three orifices also can occur if the left circumflex coronary artery arises from a separate orifice in the left coronary cusp. Four coronary orifices will be found if there are separate origins of both the right conus artery and the left circumflex coronary artery. In 1 out of 200 cases, the left circumflex coronary artery arises from the right aortic sinus of Valsalva and travels posterior to the aorta to reach its area of distribution.[2] This anomaly can be important during cardiac operation because, if it is unrecognized, the left circumflex can be damaged inadvertently.

The coronary artery ostia usually are located just below the junction of the sinus and tubular portions of the aorta or within 1 cm above this position in adults.[3] Banchi noted that the left coronary artery arose at the level of free margin of the aortic cusp in 48% of cases, above that level in 34%, and below it in 18%.[4] The right coronary artery arose at the level of the free margin of the aortic cusp in 71% of cases, above in 19%, and below in 10%.

MAJOR CORONARY ANOMALIES

Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery

Anomalous origin of the left coronary artery from the pulmonary artery (ALCA) is perhaps the most frequent important coronary anomaly with which pediatricians and pediatric cardiologists must deal. It was described by Brooks in 1886[5] and by Abbott in 1908.[6] Abbott's patient died at 60 years of age. In 1933, Bland, White,

and Garland[7] observed an infant with this anomaly and noted episodes of acute distress in the infant during feeding, presumably a manifestation of acute coronary insufficiency. ALCA occurs in 1 out of 300,000 children and constitutes 0.24% of all congenital cardiac defects.[8]

ALCA most commonly occurs as an isolated malformation. However, it has been associated with ventricular septal defect, endocardial cushion defect, tetralogy of Fallot, and truncus arteriosus.[9–14] In addition to ALCA, the left anterior descending or circumflex coronary artery may arise anomalously from the pulmonary artery.

Usually, the anomalous coronary artery arises from the left pulmonary artery sinus. However, it may arise from the right or left pulmonary artery. There are two theories of embryonic development to explain the occurrence of ALCA.[15] The first implies that the coronary arteries originate from two primordial buds on the undivided conotruncus. As the conotruncus is divided into the aorta and pulmonary artery, abnormally high placement of one of the coronary buds can result in anomalous left coronary artery (Fig. 83–3). Alternatively, abnormal division of the conotruncus can produce ALCA despite normal placement of both primordial buds (Fig. 83–3).[16,17] The second theory implies that six coronary buds or anlagen exist on the primitive truncus arteriosus: one from each potential cusp of the aortic and pulmonary sinuses. Normally, all but two involute; if, for reasons that are unclear, the wrong sequence of persistence and involution occurs, ALCA may result.[18]

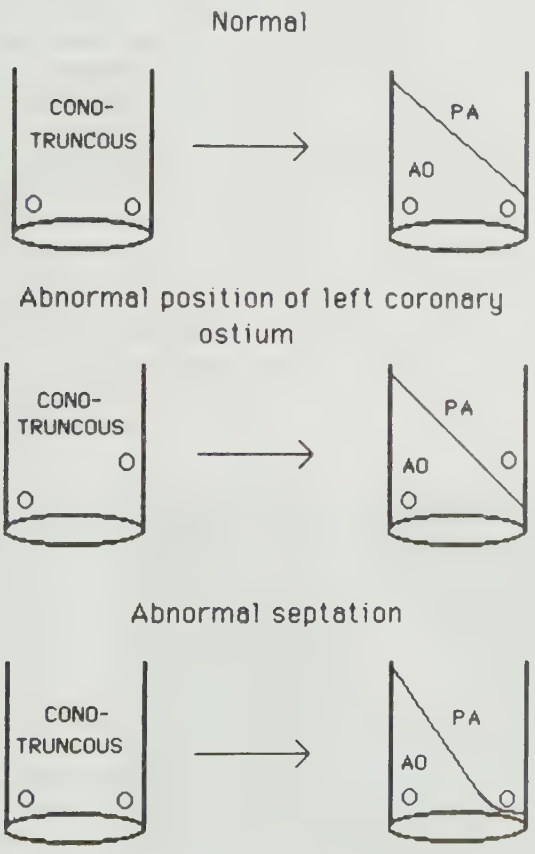

Fig. 83–3. Embryologic origin of anomalous origin of the left coronary artery from the pulmonary artery. If the left coronary artery bud is displaced cephalad, it remains with the pulmonary artery after normal conotruncal division. Alternatively, if the left coronary bud is normally located but conotruncal septation is abnormal, the left coronary artery originates from pulmonary artery. AO = aorta; PA = pulmonary artery. (Adapted from Hu, A., et al.: Coronary artery anomalies. Circulation, *30*:927, 1964.)

Clinical Manifestations

A patient with ALCA may present with signs and symptoms of myocardial infarction and congestive heart failure in infancy, or the condition may be unassociated with myocardial infarction or symptoms of heart disease and may be detected serendipitously in adulthood or at autopsy. Because of the wide range of clinical presentation and ages at presentation, investigators have divided this anomaly into two types: infantile and adult. Neufeld and Schneeweiss[3] reviewed 460 cases of ALCA reported in the literature and found that 60 (13%) of these patients presented in adulthood. This division may be arbitrary and may obfuscate the pathophysiologic features of this anomaly. The "infantile" and "adult" forms are on opposite ends of the spectrum of ALCA. The location of an individual patient within that spectrum depends on the degree of collateral circulation between the right and left coronary artery systems. Subjects with well-developed collateral connections may not develop myocardial infarction and may do well, but subjects with poor collateral circulation will have myocardial infarction, and this will be apparent at an early age. Indeed, confusion regarding the efficacy of treatment of this condition exists, to a large extent, because the natural history of the anomaly is different for different subsets of patients, and these subsets are probably based on the degree of right and left coronary artery collateral development. Results of treatment may depend on which subsets are selected for which treatment regimens.

In the immediate newborn period, pulmonary artery resistance and pressure are increased, flow through the anomalously arising left coronary artery is antegrade from the pulmonary artery, and myocardial perfusion is adequate. As pulmonary artery resistance and pulmonary pressure decrease, antegrade flow of blood from the pulmonary artery through the left coronary artery decreases. If there is inadequate collateral circulation between the right and left coronary artery, myocardial infarction will likely occur at this time. If collateral circulation exists, myocardial infarction may or may not occur, depending on the degree of retrograde flow from the right coronary system through the collateral circulation and into the pulmonary artery (i.e., coronary steal phenomenon) and the degree of antegrade flow along the distribution of the left coronary artery (i.e., myocardial perfusion).

Patients with ALCA may present in infancy and early childhood with signs and symptoms of congestive heart failure. These include tachypnea, pallor, and poor feeding. As described by Bland, White, and Garland,[7] there may be a history of paroxysms of crying, pallor, diaphoresis, and agitation in infancy, presumably due to acute myocardial ischemia. However, in many cases, these paroxysms are not described. Signs of congestive heart failure are apparent at physical examination. An apical gallop rhythm and a murmur of mitral insufficiency may be heard. Cardiomegaly is apparent on chest radiographs, and the electrocardiogram may reveal evidence of myocardial infarction. (See Chapter 45.) The clinical features of ALCA in infancy are similar to those of myocarditis and cardiomyopathy, and the diagnosis of ALCA must

be considered in the differential diagnosis of unexplained congestive heart failure in infancy.

In teenagers and adults, the presence of ALCA may be suspected on the basis of unexplained cardiomegaly, mitral insufficiency, or a continuous cardiac murmur. Angina may occur secondary to a coronary steal phenomenon.

Before the development of high-resolution, two-dimensional echocardiography and Doppler techniques, angiography was necessary to establish the diagnosis of ALCA. Injection of contrast into the aortic root reveals the origin of only a large right coronary artery from the right aortic sinus of Valsalva (Fig. 83–4). Injection of contrast into the pulmonary artery may reveal the abnormal origin of the left coronary artery, but most frequently it will not be apparent because of lack of antegrade flow from the pulmonary artery to the left coronary artery. The diagnosis also can be inapparent during aortic root angiography. The left coronary artery may fill rapidly from the right coronary artery and may *appear* to originate from the left coronary cusp. If, in addition to anteroposterior and lateral views, left and right oblique views are obtained, it will be apparent that the origin of the left coronary artery is from the pulmonary artery rather than the aorta. Visualization of ALCA can be difficult when it is associated with other intracardiac defects that produce a left-to-right shunt.

With the increasing technical sophistication of two-dimensional echocardiography, ALCA artery can be defined in many cases by using this technique. In addition, Gutgesell, Pinsky, and DePuey[19] found that thallium-201 myocardial imaging was useful in distinguishing patients with myocardial dysfunction and ALCA from patients with cardiomyopathy.

Treatment

The ideal treatment of ALCA would be to detect the presence of this anomaly before myocardial infarction occurs and to establish a coronary system that would prevent myocardial infarction. Unfortunately, all cases in infancy come to medical attention only after myocardial ischemia and infarction have occurred. In addition, as was noted above, because of the wide spectrum of myocardial compromise, it is difficult to assess results of various treatment regimens. It seems clear, however, that infants with ALCA and poor left ventricular function (an ejection fraction less than 20%) do poorly regardless of surgical or medical management at a young age.[20] Second, infants with ALCA and good left ventricular function continue to do well regardless of whether the operation is performed before or after one year of age. Third, occasionally infants who are doing poorly have spontaneous improvement (Fig. 83–5). These observations are important in designing treatment strategies to allow survival of patients with ALCA. Besides survival, however, treatment has to be directed at preservation of myocardial function. In addition, treatment strategies related to early or delayed surgical intervention need to change as surgical techniques improve. With increasing surgical experience to reimplant coronary ostia in infants with transposition of the great arteries (the Jatene procedure), the operative risk of infants with ALCA may decline.

Numerous operative techniques have been described for treatment of patients with ALCA.[14,20,22–25] These include ligation of the left main coronary artery, the Vineberg procedure, subclavian-to-left coronary artery anastomosis, saphenous vein bypass grafting, creation of an aorticopulmonary window and a tunnel to connect the aorta to the orifice of the left coronary artery, and reimplantation of the ostia of the left coronary artery onto the aorta. Ligation of the left coronary artery and the Vineberg procedure are of historical interest only and probably should be abandoned. Although there is limited scientific evidence to support the contention that a two-coronary artery system is superior to a one-coronary artery system, this concept is intuitively reasonable, and attempts to establish a two-coronary artery system for patients with ALCA seem warranted. It is unclear whether or not any one of the above procedures designed to establish a two-coronary artery system is superior to the others. The surgeon should probably use the technique with which he or she is most comfortable.

For children older than one year of age, adolescents, and adults,

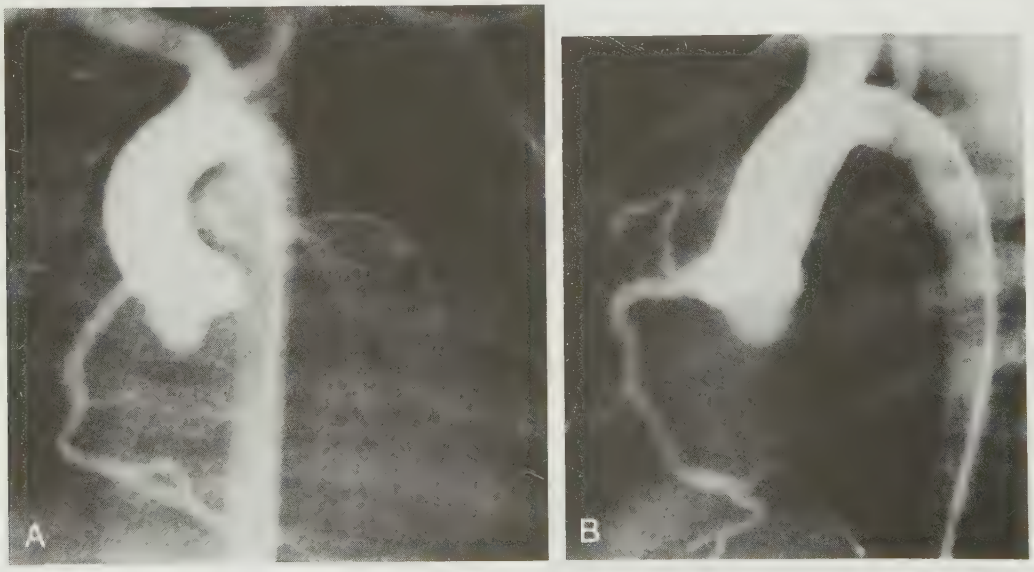

Fig. 83–4. An aortogram revealing origin only of a right coronary artery from aortic sinuses of Valsalva in a patient with anomalous origin of the left coronary artery from the pulmonary artery. (a) Anteroposterior view. (b) Lateral view.

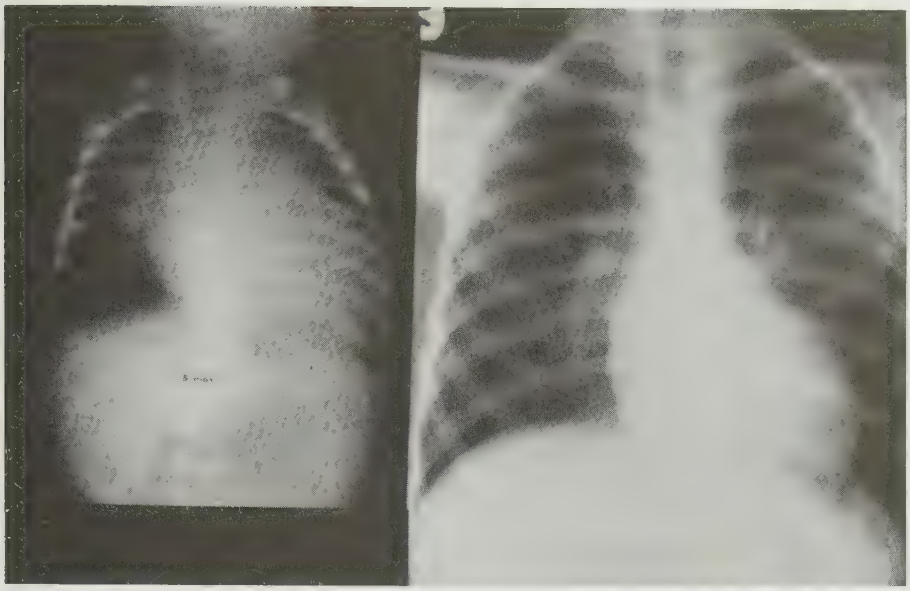

Fig. 83–5. Chest roentgenograms from patient with anomalous origin of left coronary artery from the pulmonary artery. (Left: eight months of age; right: six years of age.) Without operation, there has been spontaneous reduction of heart size and clinical improvement over 5½ years.

it is reasonable to perform an operation to establish a two-coronary artery system when ALCA is discovered. In infants (younger than one year of age) with ALCA and good left ventricular function (an ejection fraction greater than 20%), and who are doing well, it is reasonable to delay surgical correction until at least one year of age. For infants with poor left ventricular function (an ejection fraction less than 20%), it seems reasonable to intervene surgically because the natural history of the disorder in these children is poor. As surgical techniques improve and there is improvement in the survival of infants who are doing poorly (less than 1 year of age with an ejection fraction less than 20%), one might consider operating on all infants with ALCA, even those who are doing well.

At present, patients with ALCA and evidence of congestive heart failure benefit from treatment with digitalis and diuretics. Infants with evidence of acute myocardial infarction should be treated with oxygen, sedation, rest, digitalis, and diuretics.

Anomalous Origin of the Right Coronary Artery from the Pulmonary Artery

Anomalous origin of the right coronary artery from the pulmonary artery is much less frequent than ALCA.[3,26–29] The anomalous right coronary artery usually arises from the right pulmonary artery sinus and follows the distribution of a normal right coronary artery. In addition to anomalous origin of the entire right coronary artery from the pulmonary artery, branches of the right coronary artery, such as the conus artery, may arise anomalously from the pulmonary artery.

Because of the relative rarity of anomalous origin of the right coronary artery from the pulmonary artery, it is unclear whether or not it is associated with significant morbidity or mortality. Most patients are asymptomatic, but there have been several cases in which the anomaly may have been associated with cardiac arrest and death. Unlike ALCA, origin of the right coronary artery from the pulmonary artery does not cause myocardial infarction and congestive heart failure in infants and young children. A continuous or to-and-fro murmur may be a clue to the presence of this anomaly. Because of the *possible* association of anomalous origin of the right coronary artery from the pulmonary artery with sudden death, operative repair is usually recommended.[26,27]

Anomalous Origin of Both Coronary Arteries from the Pulmonary Artery

Anomalous origin of both coronary arteries from the pulmonary artery is incompatible with life unless associated anomalies exist to maintain adequate myocardial perfusion.[15,30–32] At the time of Heifetz and associates' review,[15] 25 cases of this anomaly had been reported. Seventeen of the 25 patients had additional cardiovascular anomalies, including atrial septal defect, ventricular septal defect, tetralogy of Fallot, and pulmonary atresia. All patients reported with this condition have died. Those without associated cardiac anomalies usually die within several days of birth. If anomalous origin of both coronary arteries from the pulmonary artery is associated with other cardiac malformations and its presence is apparent, surgical correction is technically feasible.

Anomalous Origin of the Left Coronary Artery from the Right Sinus of Valsalva

Anomalous origin of the left coronary artery from the right sinus of Valsalva or from the proximal right coronary artery is a rare but important malformation because it is associated with sudden death (Fig. 83–6).[33–36] After arising from the right sinus of Valsalva, the left coronary artery follows one of four routes:

1) anterior to the pulmonary artery,
2) posterior to the aorta,
3) in the ventricular septum beneath the right ventricular infundibulum,
4) between the aorta and pulmonary artery.[33]

Patients in whom the left coronary artery passes between the aorta and pulmonary artery appear to be at the greatest risk for sudden death. Sudden death is presumably due to myocardial ischemia as a result of compression of the left coronary artery between the aorta and the pulmonary artery and compromise of the lumen of the left coronary artery due to acute angulation near its origin. Cheitlin, DeCastro, and McAllister[36] reviewed 33 autopsy cases of this anomaly and found that death was sudden and un-

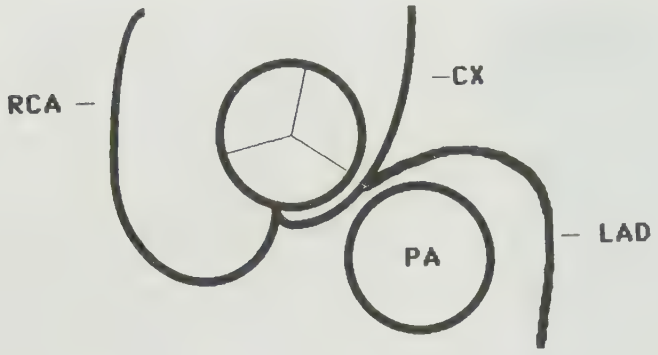

Fig. 83–6. Origin of the left coronary artery from the right aortic sinus of Valsalva. When the left coronary artery passes between the aorta and the pulmonary artery, there is risk of sudden death. CX = circumflex; LAD = left anterior descending artery; PA = pulmonary artery; RCA = right coronary artery.

expected in 27.3%.[37] Besides hypertrophic cardiomyopathy, anomalous origin of the left coronary artery from the right sinus of Valsalva is one of the more common cardiac anomalies associated with sudden unexpected death in adolescents and young adults. Unfortunately, the patients are usually asymptomatic until sudden death occurs. However, some patients may have symptoms of angina or coronary insufficiency. Symptoms may include syncope or light-headedness associated with exercise. Certainly this diagnosis must be considered in children and adolescents with angina-like chest pain, syncope, or presyncope. If this condition is suspected, exercise testing may reveal electrocardiographic evidence of ischemia, but a normal result of exercise study does not exclude the diagnosis. Coronary angiography is necessary to establish or exclude the diagnosis. However, in the future, diagnosis of this anomaly may be possible by using high-resolution echocardiography. When the left coronary artery passes between the aorta and the pulmonary artery, operative repair is indicated to prevent sudden death.

Anomalous Origin of the Right Coronary Artery from the Left Sinus of Valsalva

Anomalous origin of the right coronary artery from the left sinus of Valsalva is detected less frequently than is anomalous origin of the left coronary artery from the right sinus of Valsalva.[33,36] It may be a rarer anomaly, or it may be overlooked at the time of autopsy. If unassociated with symptoms, it may be underrepresented in coronary angiography series. Except for anecdotal cases, this anomaly is not associated with symptoms of myocardial ischemia or sudden death. Operative repair of this anomaly is indicated if signs and symptoms of myocardial ischemia are present and there are no other apparent causes for the myocardial ischemia.[3,33]

Single Coronary Artery

Single coronary artery is found in approximately 3 out of 1056 coronary angiographic studies[37,38] and 3 out of 214 patients with coronary artery anomalies.[39] It has been associated with transposition of the great arteries, coronary artery fistula, and bicuspid aortic valve. The male-to-female ratio is 1.4:1.[40] It was noted by Thebesius in 1716[41] and by Hyrtl in 1841.[42] Single coronary artery was classified by Smith[43] into three patterns: the single coronary artery predominantly followed the course of one coronary artery, either the right or left, to supply the entire myocardium; or divided to give rise to branches that distributed along normal courses of both the right and left coronary arteries; or followed a distribution that was dissimilar to the course of either the normal left or right coronary artery.

There have been three theories to explain the embryonic origin of single coronary artery: 1) congenital absence of one coronary artery anlage, 2) misplacement of one coronary artery anlage so that the misplaced anlage fused with the normally positioned anlage, and 3) abnormal closure of a coronary anlage.[44]

The clinical significance of a single coronary artery is unclear.[45–47] Kelley noted that patients in whom the single coronary artery arose from the right coronary sinus with a connecting branch that traveled between the aorta and the pulmonary artery and then distributed in the location of a normal left coronary artery were at risk for sudden death caused by the acute angulation of the connecting branch. This is similar to the situation when origin of the left coronary artery is from the right sinus of Valsalva.[48]

CORONARY ARTERY PATTERNS ASSOCIATED WITH CONGENITAL HEART DEFECTS

Tetralogy of Fallot

Although only 4 to 5% of patients with tetralogy of Fallot have associated coronary artery anomalies, it is important to recognize these abnormalities so that damage to essential coronary arteries is avoided during operative repair of tetralogy of Fallot.[49,50] Origin of the left anterior descending coronary artery from the right coronary artery occurs in 4% of patients with tetralogy of Fallot. Usually, when the left anterior descending coronary artery originates from the right coronary artery, it passes across the right ventricular outflow tract. Inadvertent division of this vessel must be avoided when right ventriculotomy is performed. Single coronary artery is the second most frequent coronary anomaly associated with tetralogy of Fallot.[50] The single coronary artery may originate from the right or left sinus of Valsalva, and the branch to the right side of the heart or the branch giving rise to the left anterior descending coronary artery and circumflex coronary artery may cross the right ventricular outflow tract and be at risk for inadvertent damage at the time of ventriculotomy. Forty percent of cases of tetralogy of Fallot have a long, large right conus artery that distributes to a significant mass of myocardium. Although this does not represent a true coronary anomaly, it is important to be aware of a large conal artery and avoid its division during repair of tetralogy of Fallot.

Additional coronary anomalies that are observed in tetralogy of Fallot include origin of the right coronary artery from the posterior sinus of Valsalva, origin of the right coronary artery from the pulmonary artery, origin of the left coronary artery from the pulmonary artery, origin of the left coronary artery from the posterior coronary sinus of Valsalva, and an accessory coronary artery originating from the posterior aortic sinus of Valsalva.[3]

Transposition of the Great Arteries

There are two major coronary artery patterns in "complete" or "simple" or "d-transposition" of the great arteries.[3,51,52] Most

commonly, the right coronary artery arises from the posterior aortic sinus, and the left coronary artery arises from the left coronary sinus and divides into a circumflex and anterior descending coronary artery (Fig. 83–7). The right aortic sinus of Valsalva is the noncoronary cusp. This pattern occurs in two thirds of cases of d-transposition of the great arteries and is most common when the aorta and pulmonary artery are obliquely oriented (aorta to the right and anterior to the pulmonary artery).

In the second coronary artery pattern, the right coronary artery arises from the posterior aortic sinus and gives rise to the circumflex coronary artery, which passes posterior to the pulmonary artery. The anterior descending coronary artery arises from the left coronary sinus, and the right aortic sinus of Valsalva is the noncoronary sinus. This pattern is present in one third of patients with d-transposition of the great arteries and is most commonly associated with great arteries that are in a side-by-side relationship.

Variations of the above pattern occur, including origin of both coronary arteries from the posterior aortic sinus; separate origin of the circumflex coronary artery from the posterior aortic sinus; dual circumflex coronary arteries arising from both the right and left coronary arteries; and dual descending coronary arteries, the second arising from a circumflex coronary artery that arises from the right coronary artery; and single coronary artery.[3]

L-Transposition of the Great Arteries

The aorta is anterior and to the left of the pulmonary artery in l-transposition of the great arteries (''corrected transposition of the great arteries'' or ''ventricular inversion''). One aortic sinus of Valsalva is oriented anteriorly (anterior sinus of Valsalva), one posteriorly and rightward (right sinus of Valsalva), and one posteriorly and leftward (left sinus of Valsalva). The right coronary artery originates from the right aortic sinus of Valsalva and divides into an anterior descending branch that follows the course of the interventricular sulcus (Fig. 83–8). The right coronary artery coninues to follow a course in the right atrioventricular sulcus. The left coronary artery originates in the left aortic sinus of Valsalva and follows the course of the circumflex coronary artery in the left atrioventricular sulcus. The left (''circumflex'') coronary artery produces a marginal branch and continues as the posterior descending coronary artery.[3]

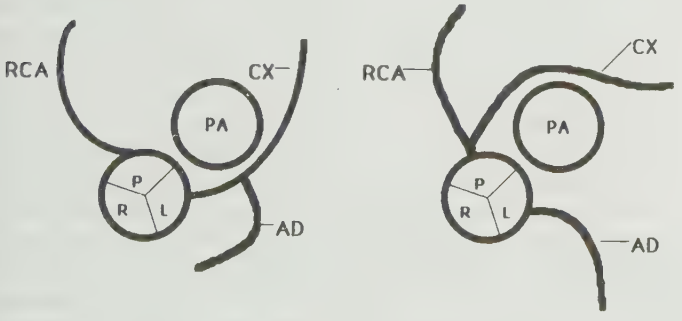

Fig. 83–7. Coronary artery patterns in d-transposition of great arteries. The pattern on the left is most commonly found when the great arteries are obliquely related. The pattern on the right is more common when great arteries are in a side-by-side relationship. CX = circumflex; AD = anterior descending artery; RCA = right coronary artery; AD = anterior coronary artery; P, R, L = posterior, right, and left aortic cusps.

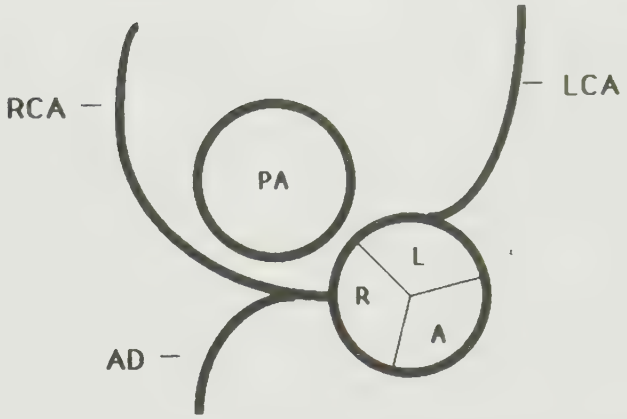

Fig. 83–8. Coronary artery pattern of l-transposition of the great arteries (''ventricular inversion'' or ''corrected transposition''). RCA = right coronary artery; PA = pulmonary artery; AD = anterior descending artery; LCA = left coronary artery; R, L, A = right, left anterior aortic cusps.

Double-Inlet Left Ventricle

Double-inlet left ventricle exists with a subaortic outlet chamber located either anteriorly and to the left or anteriorly and to the right. This outlet chamber is a rudimentary right ventricle that receives no atrioventricular valve and has no atrioventricular valve support apparatus. The outlet chamber communicates with the ''single'' left ventricle via a ventricular septal defect or ''bulboventricular foramen.'' The coronary artery pattern depends on the location of the outlet chamber and the spatial relationships of the aorta and pulmonary artery.[53,54]

When the outlet chamber is anterior and to the right, the aorta lies anterior and to the right of the pulmonary artery. In these instances, the right coronary cusp is the noncoronary sinus of Valsalva. The right coronary artery arises from the posterior aortic sinus of Valsalva and courses in the right atrioventricular sulcus. The left coronary artery arises from the left aortic sinus of Valsalva and gives rise to an anterior descending coronary artery that follows the interventricular sulcus and a left circumflex coronary artery that courses in the left atrioventricular groove. Lev and associates[53] and Keeton and associates[54] described slightly different coronary patterns in which the left coronary artery gave rise to a ''left delimiting'' artery (instead of a left anterior descending coronary artery), and the right coronary artery also gave rise to a ''right delimiting'' artery. These two delimiting arteries border the outlet chamber.

When the outlet chamber is anterior and to the left, the aorta is anterior and to the left of the pulmonary artery (Fig. 83–9). Elliot and associates[55] described two distinct coronary artery patterns. In both, the anterior aortic sinus of Valsalva was the noncoronary cusp. In the first pattern, the right coronary artery arose from the right aortic sinus of Valsalva and coursed in the right atrioventricular groove. The left coronary artery arose from the left aortic sinus of Valsalva and divided into an anterior descending coronary artery and a circumflex coronary artery. In the second pattern, the anterior descending coronary artery arose from the right coronary artery rather than the left coronary artery. Lev and associates[53] described two delimiting arteries that bordered the

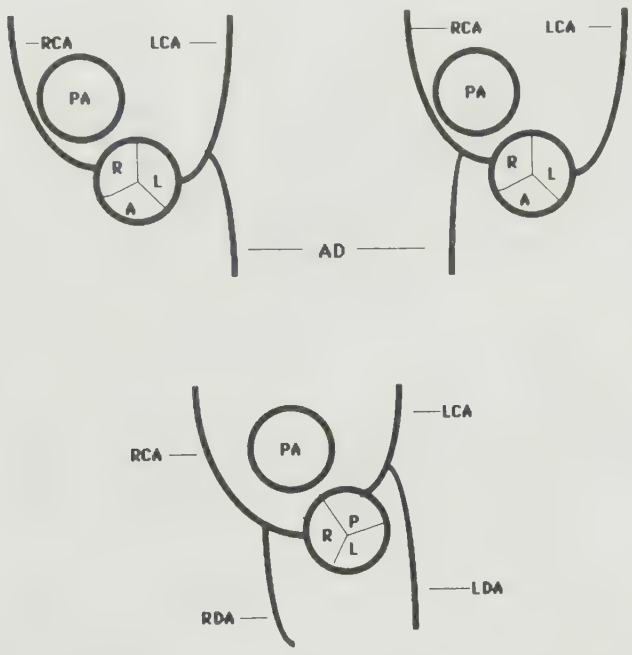

Fig. 83–9. Coronary artery pattern in a double-inlet left ventricle (univentricular heart) with a subaortic outlet chamber located anteriorly and leftward. RCA = right coronary artery; LCA = left coronary artery; PA = pulmonary artery; RDA = right delimiting artery; LDA = left delimiting artery; P, R, L = posterior, right, and left aortic cusps.

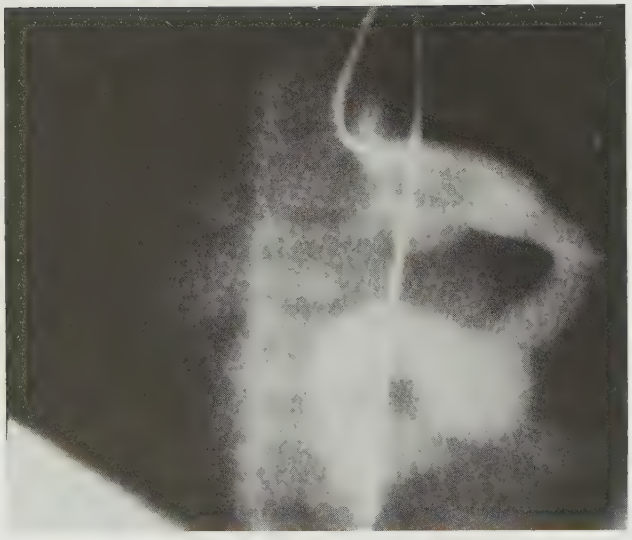

Fig. 83–10. A cineangiogram of a dilated and tortuous right coronary artery resulting from coronary artery fistula.

outlet chamber: one arising from the left and one from the right coronary artery.

Double-Outlet Right Ventricle

Usually, the coronary artery pattern in double-outlet right ventricle is normal. However, Neufeld and Schneeweiss[3] described nine separate variations of coronary anatomy in double-outlet right ventricle. Details are given in their excellent review.[3]

Truncus Arteriosus

Various coronary artery patterns occur in truncus arteriosus depending on the number of aortic valve cusps and the spatial rotation of the truncus.[3,56,57] In general, the left coronary artery arises from the left posterior cusp and the right coronary artery from the right anterior cusp. There may be a single coronary artery, or two ostia may arise in close proximity. It is important to recognize atypical coronary artery patterns and the presence of large diagonal branches of the right coronary artery that course over the entry surface of the right ventricle. These vessels are subject to injury during right ventriculotomy.

CORONARY ARTERY FISTULA

Coronary artery fistula was described by Krause in 1865[58] and Brooks in 1866.[5] Coronary artery fistula comprises 0.2 to 0.4% of congenital cardiac defects.[59] There is no apparent gender predilection. Fistulae originate equally from the right and left coronary artery systems.[3] Most commonly, the fistula connects to the right ventricular cavity via a single opening or multiple openings. The right atrium is the second most common terminus, and two thirds of those draining into the right atrium originate from the right coronary artery. A fistula can also terminate in the pulmonary artery, left atrium, left ventricle, superior vena cava, coronary sinus, or a persistent left superior vena cava. The involved coronary artery is usually dilated (Fig. 83–10), and the chamber in which the fistula terminates may be enlarged. In childhood and adolescence, the fistula usually does not produce symptoms, but signs and symptoms of congestive heart failure can occur secondary to a large left-to-right shunt. The presence of a fistula is usually detected from the presence of a continuous precordial murmur. There may be a precordial thrill, decreased diastolic blood pressure, and widened pulse pressure. The physical findings may be confused with those of patent ductus arteriosus, but the murmur of a patent ductus arteriosus is usually heard best in the left infraclavicular area and that of a coronary artery fistula at the midleft sternal border.

Angiography is necessary to confirm the diagnosis of coronary artery fistula. The differential diagnosis includes patent ductus arteriosus, the combination of ventricular septal defect and aortic insufficiency, fenestration of a coronary artery cusp, and pulmonary or chest wall arteriovenous fistulae. It is important to identify the coronary artery involved in the fistula and branches of the coronary artery in the region of the fistula for proper planning of a surgical procedure.

The presence of a coronary artery fistula is the indication for surgical obliteration of the fistula. The purpose of eliminating the malformation is to prevent eventual congestive heart failure secondary to a left-to-right shunt, rupture of the dilated coronary artery, endocarditis, and myocardial infarction or ischemia.[3]

There are several surgical procedures designed to interrupt the fistulous tracts. Depending on the particular fistula, the operation may or may not require cardiopulmonary bypass. Particular care must be taken not to interrupt important coronary artery branches when interrupting the fistulous tract.[60,61]

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CHAPTER 84

Anomalies of Systemic Venous Return

James C Huhta

The variations of the normal human venous system and its development have been the object of anatomic study for many years.[1,2] Analysis of abnormalities of veins has become more relevant since the era of diagnostic cardiac catheterization and corrective cardiac surgery because patient treatment may depend in part on the details of the connection of the systemic veins. A descriptive approach to the systemic venous return can be accomplished by analyzing the veins returning to the heart, one at a time, in a segmental fashion (Fig. 84–1). These segments include the superior venae cavae, the coronary venous return, the inferior vena cava, the azygous veins, and the hepatic veins. Any scheme of description must describe the presence or absence of the segment and the connection of the segment.

Atrial situs is a key variable in the understanding of venous development. Additional discussion of situs can be found in Chapter 75. If there is lateralized situs (situs solitus or inversus), then the spectrum of abnormalities that one expects is limited and fairly predictable. The coronary sinus is usually present, and the chance of any significant abnormality is low. However, if there is abnormal situs with heterotaxy and isomeric atria, then abnormal atrial anatomy (common atrium) and the connections of venous segments are fundamentally flawed. ''Abnormalities'' are common and bizarre but predictable depending on the situs. Associations of the venous abnormalities with the various types of situs described above are summarized in Figure 84–2. One may conclude that an abnormality in situs solitus may be common with an unusual type of situs. Connection problems with the superior venae cavae, for example, are extremely rare in situs solitus but are expected in left and right atrial isomerism.[3]

EMBRYOLOGY

Paired development of the venous system is present in early stages and includes bilateral venous structures in the umbilical, vitelline, and cardinal areas. The umbilical and vitelline veins in the 13 somite stage drain bilaterally into the right and left sides of the common atrium, forming the left and right horns of the sinus venosus (the inferior wall of the common atrium). By the 20 somite stage, in situs solitus, the anterior and posterior cardinal veins (bilateral confluences called the left and right common cardinal veins) are incorporated into the respective horns of the sinus venosus (Fig. 84–3). Lateralization in venous return appears to occur by two processes: (1) invagination of the left sinus horn separating it from the left atrium and (2) rightward shift of the sinus venosus. These events lead to separation of the left horn of the sinus venosus from the developing left atrium and lateralization of all the systemic venous return to the right atrium. The hepatic veins develop from the confluence of the left and right omphalomesenteric veins, which form one confluence in the lateralization of the sinus venosus to the right. The anterior cardinal system that will drain the upper body results in the superior venae cavae, and normally, the left anterior cardinal vein regresses so that the left innominate vein (which has developed to connect the anterior cardinal veins) enlarges. The left common cardinal vein remains to drain the coronary circulation only (the coronary sinus). Obliteration of the left anterior cardinal vein results in a remnant called the ligament of Marshall and the left superior intercostal vein (dotted line in Fig. 84–3).

The embryology of the inferior vena cava (Fig. 84–4) is final-

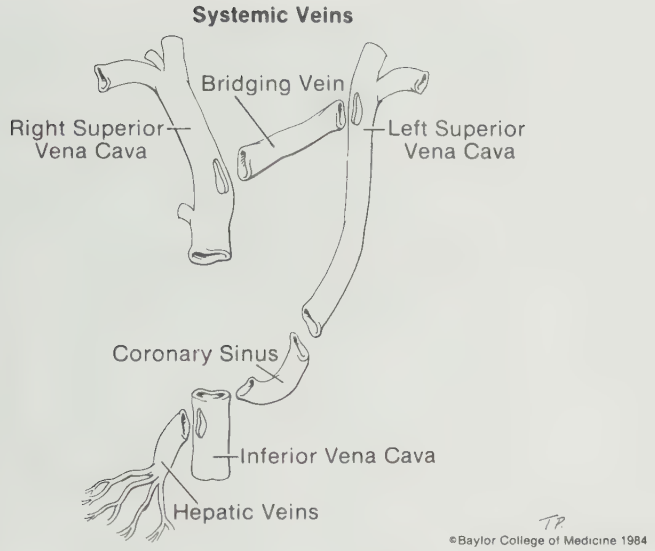

Fig. 84–1. Normal systemic venous segments. (Copyright © Baylor College of Medicine 1984. Used with permission.)

ized slightly later (between six and eight weeks of development) and forms by shifting of the venous return from the bilateral posterior cardinal system to a central confluence of veins (the inferior vena cava). The posterior cardinal system drains the caudal portion of the body, and flow transfers to the subcardinal and supracardinal veins. The posterior cardinal system of veins below the diaphragm regresses completely, and anastomoses develop between the subcardinal (ventral) and supracardinal (dorsal) bilateral systems. The subcardinal system results in the inferior vena cava from the renals to the hepatics. The supracardinal system results in the inferior vena cava below the renals and the azygous and hemiazygous veins. Right-sided dominance develops from the junction of the right subcardinal and the hepatic veins and the coalescence of the above structures.

If there are bilateral isomeric atria, then the embryologic development of the venous system is altered and cannot be compared to normal development. As a consequence of the increasing body of knowledge about the spectrum of abnormalities of abdominal situs associated with atrial isomerism, the abnormalities of venous return may be only one relatively minor part of anatomy that does not reflect "normal" development in any predictable way. There is a trend toward persistence of the bilateral nature of the venous return that is present much earlier in development. Whether the regularity of venous anomalies in atrial isomerism is due to local effects after differentiation or to a very early genetic signal is not known.

SUPERIOR VENAE CAVAE

The right superior vena cava is a derivative of the cardinal venous system and drains blood from the upper half of the body (Table 84–1). This structure is formed by the junction of the two brachiocephalic veins and is without valves. It receives the azygous vein and several small veins from the pericardium and other mediastinal structures. The lower half is within the pericardium and is covered in front and on each side by the serous pericardium.

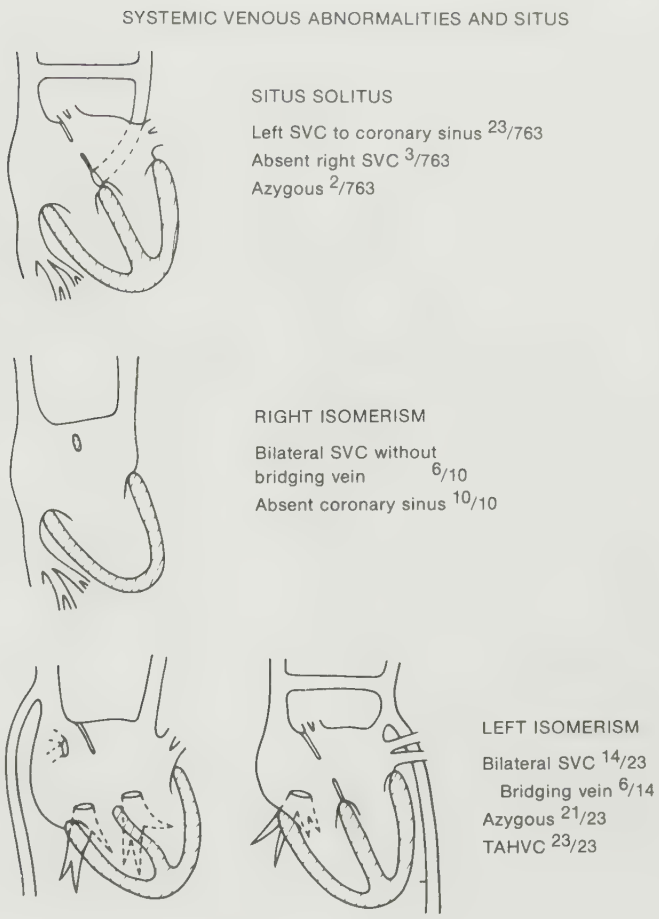

Fig. 84–2. Systemic venous abnormalities and atrial arrangement. The most common venous abnormality in situs solitus is a persistent left superior vena cava (SVC) connecting to the coronary sinus (upper panel). In right atrial isomerism, there are usually bilateral superior cavae, without a bridging vein, connecting with bilateral morphological right atria. The coronary sinus is always absent (middle panel). In left atrial isomerism, many abnormalities coexist, but all have total anomalous hepatic venous connection (TAHVC). There may be bilateral superior cavae connecting to bilateral morphological left atria, or the left SVC may connect to a coronary sinus if present. Azygous continuation of the inferior vena cava is common (lower panel). In situs inversus, the systemic venous return is a mirror image of normal. (From Huhta, J.C., et al.: Cross-sectional echocardiographic diagnosis of systemic venous return. Br. Heart J., *48*:388, 1982.)

Table 84–1. Embryologic Origin of the Major Systemic Veins

Venous Segment	*Embryologic Precursor*
Right superior vena cava	right anterior cardinal
Left superior vena cava	left anterior cardinal
Innominate vein	precardinal anastomosis
Coronary sinus	left common cardinal
Hepatic veins	omphalomesenteric
Inferior vena cava	subcardinal above renals supracardinal below renals
Azygous veins	supracardinal

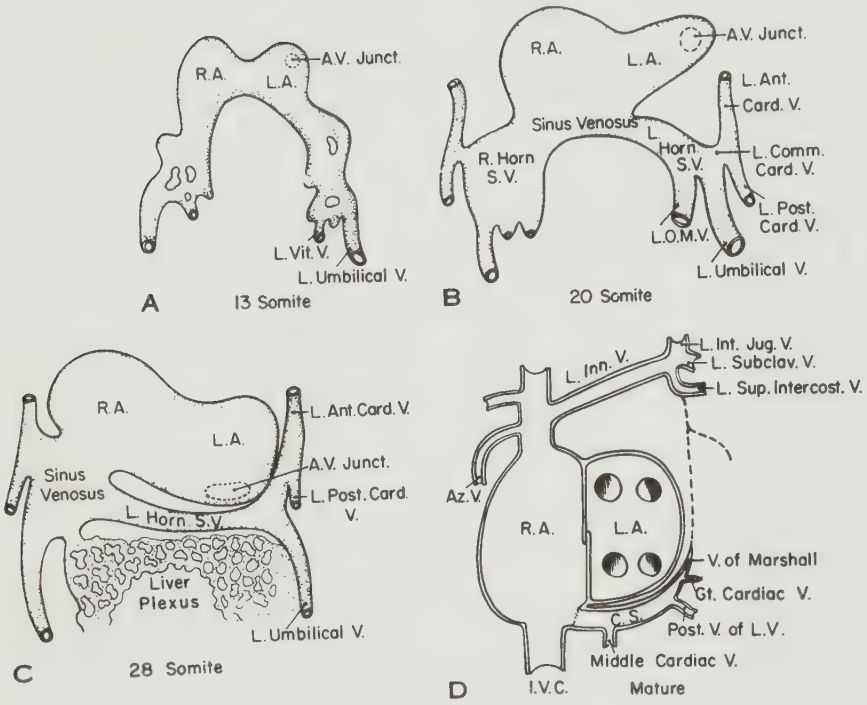

Fig. 84–3. Embryology of the cardinal venous system. (A) At 13 somite, the bilaterally symmetrical umbilical and vitelline veins drain into the right and left sides of the common atrium. (B) At 20 somite, the anterior and posterior cardinals have appeared. Asymmetrical development begins with the atrioventricular junction localized to the left side of the developing atrium and continues by the occurrence of an invagination between the left horn of the sinus venosus and the left atrium (C) finally separating these two structures and directing all systemic venous blood into the right atrium. (D) Asymmetry is continued by the development of the left innominate vein (L. Inn. V.). The common cardinal vein persists, becoming the coronary sinus (C.S.) after the left anterior cardinal vein (L. Ant. Card. V.) becomes atretic. L. Ant. Card. V. = left anterior carotid vein; L. Post. Card. V. = left posterior carotid vein; L. Comm. Card. V. = left common carotid vein; L. Umbilical V. = left umbilical vein; R.A. = right atrium; L.A. = left atrium; L. Int. Jug. V. = left internal jugular vein; L. Subclav. V. = left subclavian vein; L. Sup. Intercost. V. = left superior intercostal vein; V. of Marshall = Marshall's vein; Gt. Cardiac V. = great cardiac vein; Post. V. of L.V. = posterior vein of the left ventricle; Middle Cardiac V. = middle cardiac vein; I.V.C. = interior vena cava; Az.V. = azygous vein; L.Vit. V. = left vitelline vein; R. Horn S.V. and L. Horn S.V. = right and left horn of the sinus venosus; A.V. Junct. = atrioventricular junction; L.O.M.V. = left omphalomesenteric vein. (From Lucas, R.V., Jr., and Schmidt, R.E.: Anomalous venous connections, pulmonary and systemic. *In* Heart Disease in Infants, Children, and Adolescents. 2nd Ed. Edited by A.J. Moss, F. Adams, and G.Z. Emmanouilides. Baltimore, Williams & Wilkins, 1977.)

The shadow of its lateral border can be seen in routine chest roentgenograms.

Persistent Left Superior Vena Cava

A persistent left superior vena cava may drain via the coronary sinus to the right atrium or may drain abnormally to the left atrium, either directly with absence or unroofing of the coronary sinus or to a left pulmonary vein (partially persistent left superior vena cava). A right superior vena cava is present and may or may not communicate with the left superior vena cava. Bilateral superior venae cavae (double venae cavae) have been known to occur approximately once in every 348 autopsies[4] (Fig. 84–5). The innominate vein may be absent, small, or well developed. In general, the size of the innominate vein is inversely proportional to the size of the persistent left vena cava.[5,6] The course of a persistent left superior vena cava may be anterior to (Fig. 84–6) or posterior to the left pulmonary artery. The potential for obstruction exists in the latter case. A left superior vena cava may occur without a right superior vena cava,[7,8] in which case all the superior caval venous return drains to a greatly enlarged coronary sinus via the persistent left cava. In congenital heart disease (presumably with situs solitus), a persistent left superior vena cava was associated with tetralogy of Fallot in 20% of cases and Eisenmenger's syndrome in 8% of cases.[9]

Diagnosis of left superior vena cava may be indicated on chest roentgenogram by a shadow along the left medial border of the mediastinum. It may be suspected on clinical examination by abnormal jugular pulses.[10] Frequently, a left superior P wave axis is associated with a persistent left superior vena cava;[11] however, this is a common finding in left atrial isomerism. Echocardiography will demonstrate an enlarged coronary sinus and the anomalous vein can be detected with a sensitivity of 95 to 100%[3] (Table 84–2).

Left Superior Vena Cava Connecting to the Left Atrium

In this anomaly, the persistent left superior vena cava passes anterior to the left pulmonary artery and connects directly to the left atrium immediately below the atrial appendage and anterosuperior to the left upper pulmonary vein[12,13] (Fig. 84–7). This is most commonly associated with bilateral left or right atria. Particularly with right atrial isomerism, the coronary sinus is absent. Although this anomaly can be explained by failure of development of the coronary sinus, this explanation may not be relevant in the presence of atrial isomerism. Rarely, this defect may occur with

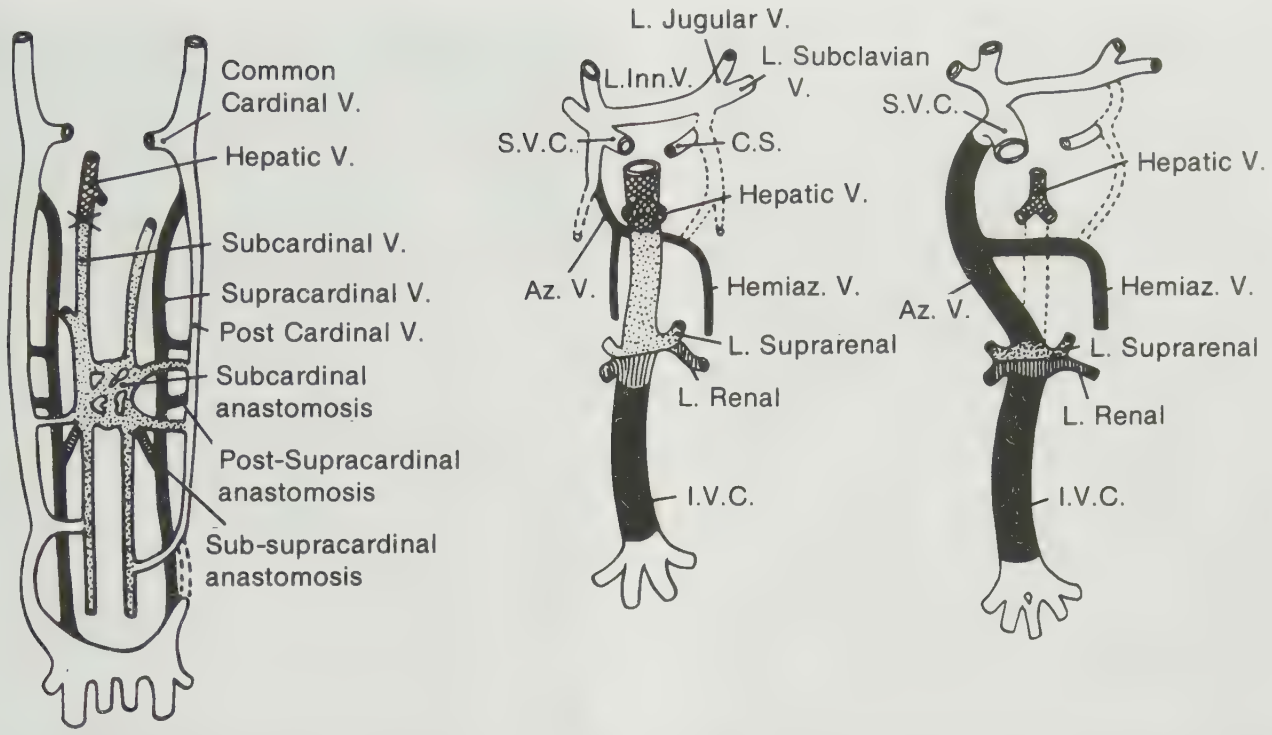

Fig. 84–4. Embryologic development of the inferior vena cava (IVC). (Left) Early stage. Venous blood from the lower body may reach the heart by way of the posterior cardinal veins (Post. Cardinal V.), the supracardinal veins, and the upper portion of the IVC, derived from hepatic and subcardinal veins. Multiple anastomotic sites between these venous systems exist in the renal area as shown. (Center) Normal development of IVC. The major venous drainage channel from the lower body is by way of the IVC, derived, from below upward, from the posterior cardinal system (white), the supracardinal system (black), the renal collar (lines), the subcardinal system (stippled), and the hepatic veins (cross-hatched). A small accessory venous channel is provided by persistence of the supracardinal veins, as hemiazygous and azygous veins. (Right) Interruption of the IVC with azygous continuation. Failure of junction of the right subcardinal vein and hepatic vein occurs and results in absence of the IVC from the region of the renal veins upward. The hepatic veins drain directly into the right atrium. All other blood from the lower body drains normally to the junction of the renal veins with the IVC and then continues by way of a greatly dilated azygous vein into the superior vena cava. L. = left; V. = vein; Inn = innominate; AZ. = azygous; SVC = superior vena cava; C.S. = coronary sinus; Hemiaz. = hemiazygous. (From Lucas, R.V., Jr., and Schmidt, R.E.: Anomalous venous connections, pulmonary and systemic. *In* Heart Disease in Infants, Children, and Adolescents. 2nd Ed. Edited by A.J. Moss, F. Adams, and G.Z. Emmanouilides. Baltimore, Williams & Wilkins, 1977.)

extensive unroofing of the coronary sinus in situs solitus. If this occurs as an isolated defect without other interatrial communication, the presentation is cyanosis early in infancy without a heart murmur. The diagnosis can be made by angiography or echocardiographic contrast injection in the left arm (see below). Surgical treatment consists of ligation if there is a bridging innominate vein or if the upper venous pressure is less than 15 mm Hg with ligation of the anomalous vena cava. Alternatively, the left superior vena cava can be reimplanted into the right atrium[14] or the pulmonary artery.[15] Today, the favored procedure is creation of an intra-atrial baffle.[16] If a common atrium is present, the entire conduction system is to the left of the baffle. The association of left superior vena cava connecting to the left atrium was one of the early observations in the heterotaxy syndrome.[17]

Right Superior Vena Cava Connecting to the Left Atrium

This rare abnormality can cause cyanosis; it can be thought of as a form of atrial septal defect with overriding of the superior vena caval entry.[18,19] The results are hemodynamically similar to connection of a persistent left superior vena cava to the left atrium.

CORONARY SINUS

Normally, the coronary sinus is a right atrial structure and is thought to be formed by invagination of the left portion of the anterior cardinal system into the left atrium. Mantini and associates summarized the rare types of coronary sinus anomalies encountered at autopsy.[20] Absence of the coronary sinus is common in atrial situs abnormalities with atrial isomerism and is distinctly uncommon with lateralized situs.[3] Atresia of the coronary sinus orifice is extremely rare[21,22] but is very important because of the possibility that ligation of a persistent left superior vena cava that drains the coronary veins could cause severe myocardial ischemia. If stenosis or atresia of the coronary sinus occurs, then the thebesian veins may provide adequate drainage of myocardial venous blood to the right atrium. Unroofed coronary sinus is a defect in the superior aspect of coronary sinus as it passes behind the left atrium, thereby creating an entry for desaturated blood into the left atrium. This defect may be associated with atrial septal defect or may occur in isolation and presents in a manner that is similar to left superior vena cava connection to the left atrium. The diagnosis can be made by contrast echocardiography (Fig. 84–8).

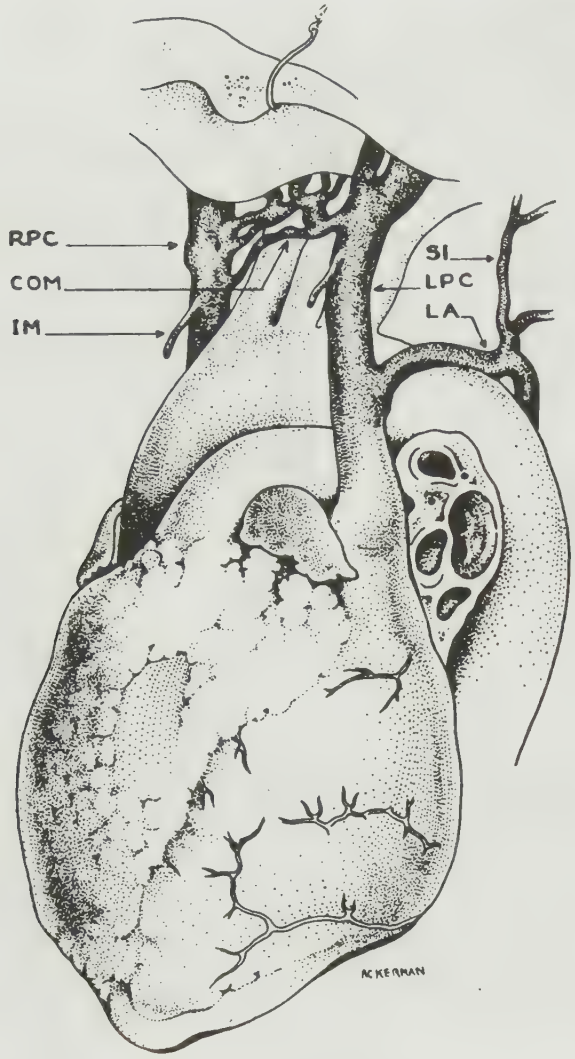

Fig. 84–5. Bilateral superior vena cavae. Left lateral view of the heart showing precavae and small cross-connection (bridging vein). COM = bridging innominate vein; IM = internal mammary; LA = left azygous; LPC = left precava; RPC = right precava; SI = superior intercostal vein. (Sanders, J.M.: Bilateral superior vena cava. Anat. Rec., *94*:657, 1946.)

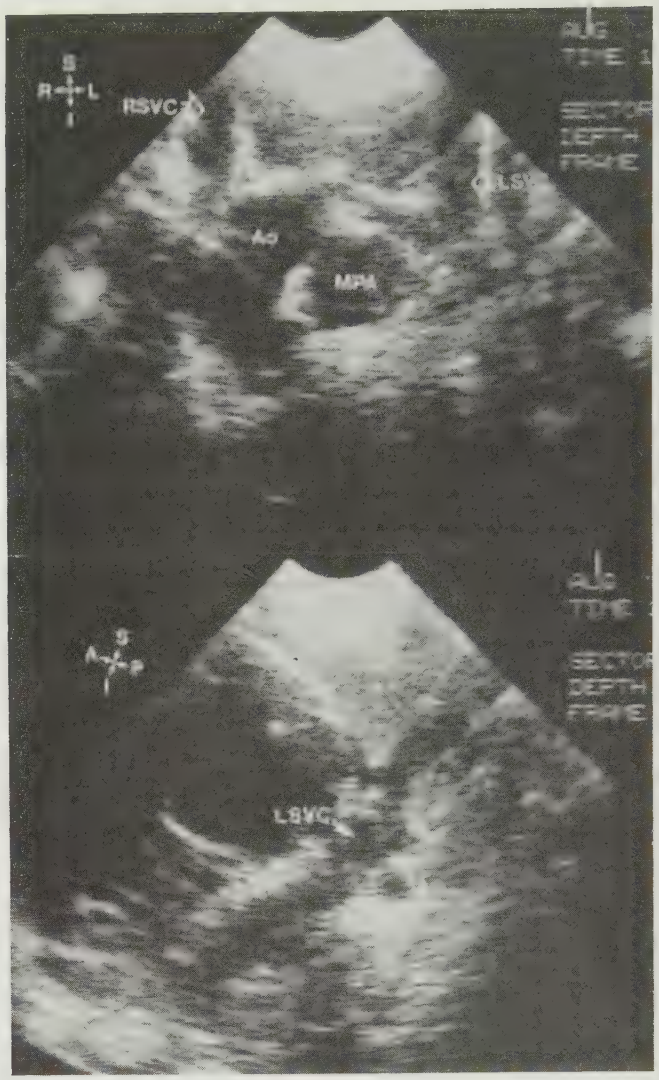

Fig. 84–6. Bilateral superior vena cavae with no bridging vein connecting them. Suprasternal scans by echocardiography show the right and left superior cavae (RSVC and LSVC) and the course of the left cava anterior to the left pulmonary artery (open arrow in the lower panel). A = anterior; Ao = aorta; I = inferior; L = left; MPA = main pulmonary artery; P = posterior; R = right.

Table 84–2. Detection of Superior Caval Segments 2-D Echocardiography vs Angiography

	800 Patients			
	Right SVC	*Left SVC*	*Bilateral SVC*	*Bridging Innom. Vein with Bilateral SVC*
2-D Echo: Yes	792	46	38	13
No	8	754	762	25
Angiography: Yes	792	48	40	18
No	8	752	760	20
Sensitivity	100%	96%	95%	72%
Specificity	100%	100%	100%	100%

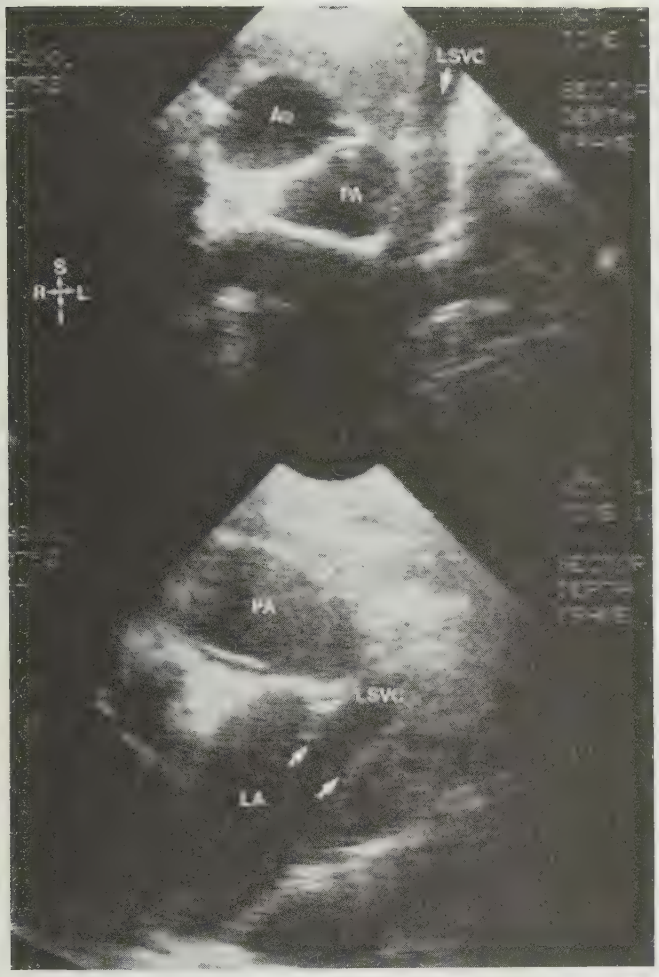

Fig. 84–7. Left superior vena cava (LSVC) connecting to the left atrium (LA) directly in a patient with left atrial isomerism. The LSVC passes anterior to the pulmonary artery. A = anterior; Ao = aorta; I = inferior; L = left; MPA = main pulmonary artery; P = posterior; R = right.

An atrial septal defect of the coronary sinus type is rare but is distinguished from a primum defect by the absence of a normal coronary sinus in the former. Rarely, the coronary sinus connects to the inferior vena cava instead of the right atrium.

INFERIOR VENA CAVA

There is a broad spectrum of variations in inferior caval return below the level of the renal veins. However, the position of the inferior vena cava superior to the renal veins is relatively constant, passing anteriorly as it ascends. Although embryologists have perceived that the portion of the inferior vena cava connecting to the heart was independent of the hepatic veins, there is no evidence to support this concept in humans. On the contrary, the occurrence of direct hepatic connection to the heart in left atrial isomerism argues against such a "segment" above the liver. The spectrum of inferior systemic venous return in 1000 consecutive patients seen in a pediatric cardiology clinic revealed a completely normal pattern in 97%[3] (Fig. 84–9). In the normal pattern, the vena cava

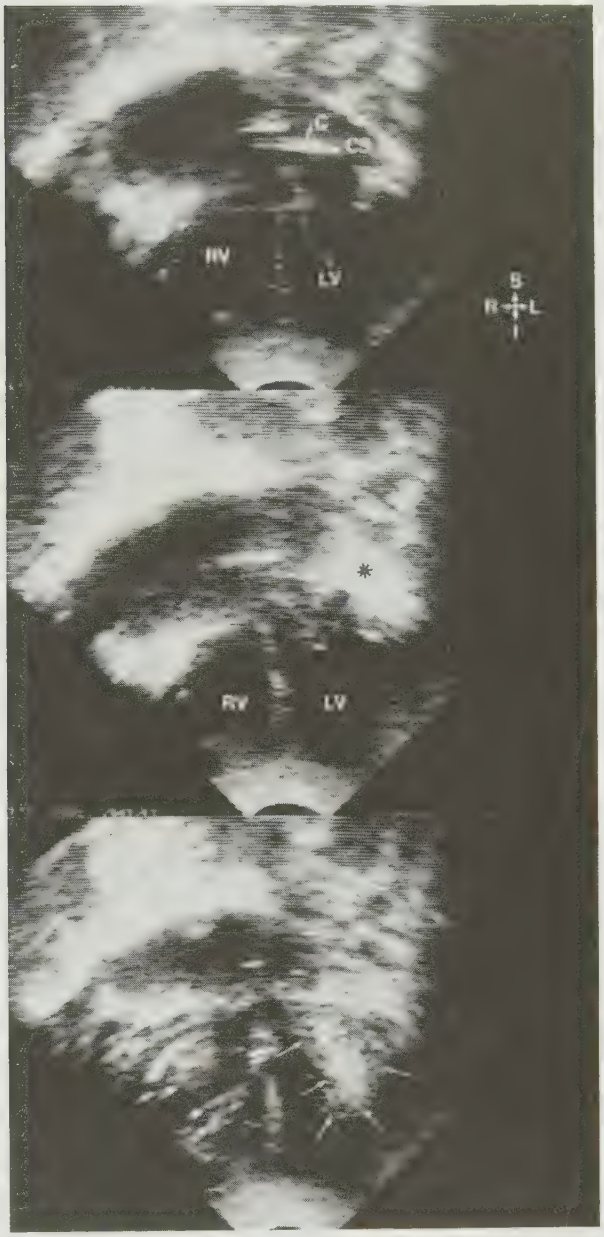

Fig. 84–8. Catheter (C) echocardiographic contrast injection in the left superior vena cava via the coronary sinus (CS) in a patient with unroofed coronary sinus. The contrast (asterisk) fills the coronary sinus in the left lateral atrioventricular groove first (middle panel), and later the mitral valve and the left ventricle (white arrows in the lower panel). I = inferior; L = left; R = right; S = superior; RV = right ventricle; LV = left ventricle.

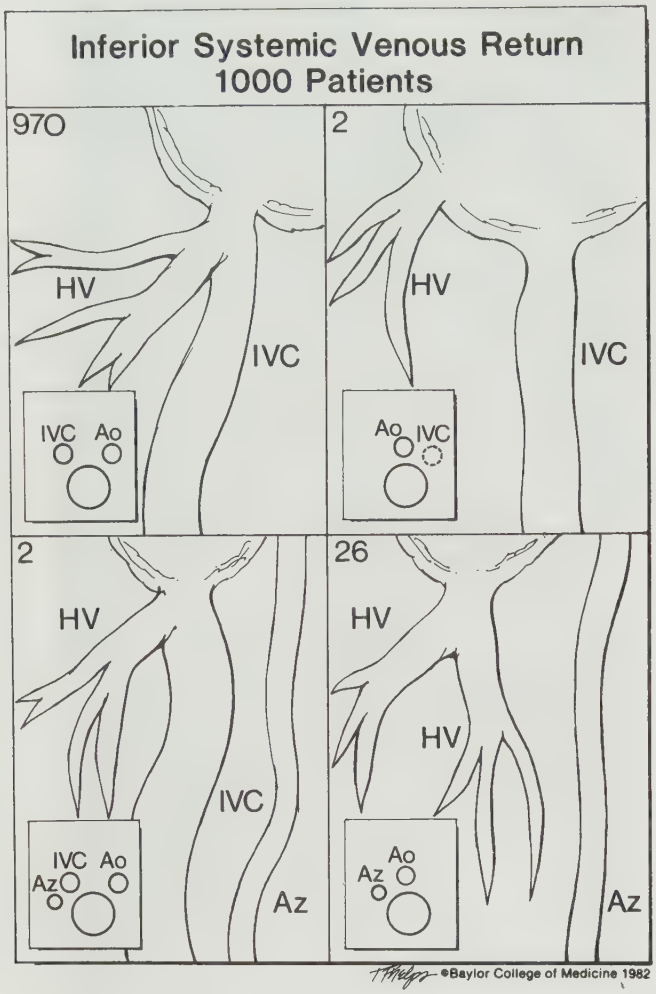

Fig. 84–9. Inferior vena caval return in a prospective study of patients with congenital heart disease. HV = hepatic vein; IVC = inferior vena cava; Ao = aorta; Az = azygous vein. (Used with permission.)

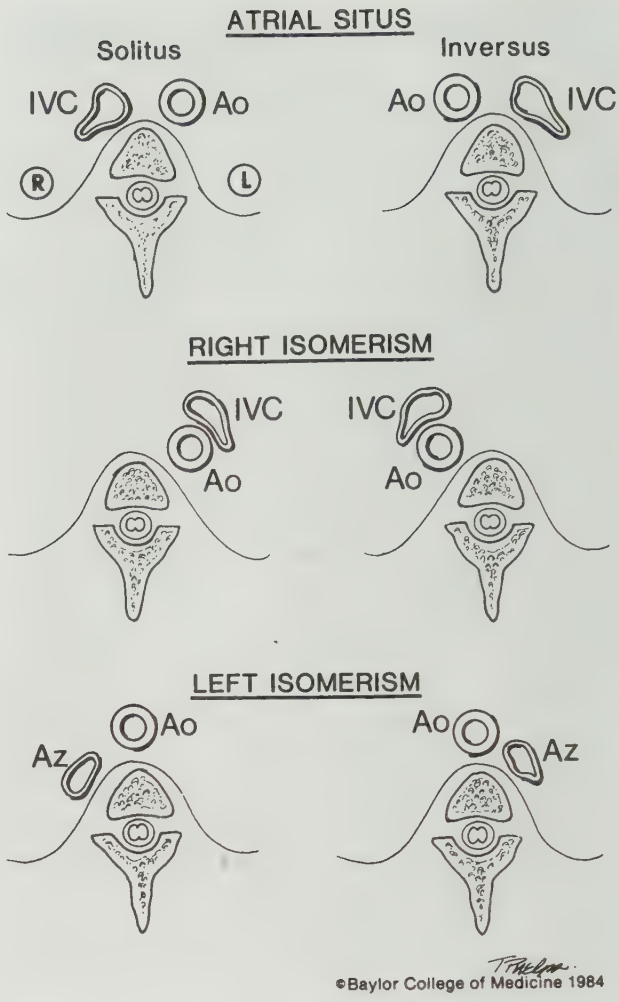

Fig. 84–10. Use of the position of the inferior vena cava for the diagnosis of atrial situs. IVC = inferior vena cava; Ao = aorta; Az = azygous vein. (Used with permission.)

is symmetrically placed to the right of the spine with the aorta to the left. Separate connection of the inferior vena cava without receiving hepatic venous connection was rare but occurred only in cases of left atrial isomerism. The location of the inferior vena cava is useful in the diagnosis of atrial situs by echocardiography (Fig. 84–10). Elliot and associates described the course of the inferior vena cava and the aorta together in patients with asplenia syndrome undergoing venous angiography.[23] Echocardiography is useful to image the inferior vena cava[24] and shows it to be lateral and anterior to the aorta on the same side in these patients with asplenia[25] (Fig. 84–11).

INTERRUPTION OF THE INFERIOR VENA CAVA WITH AZYGOUS CONTINUATION

Azygous and Hemiazygous Veins

Formed from paravertebral drainage of the right ascending lumbar vein, subcostal vein, and lumbar azygous vein (if present), the common azygous trunk ascends in the posterior mediastinum to the level of the fourth thoracic vertebra, where it arches forward above the root of the right lung and ends in the superior vena cava, just before that vessel pierces the pericardium. At this site, the azygous vein is joined by the confluence of the second, third, and fourth posterior intercostal veins, which is called the right superior intercostal vein.

The hemiazygous vein arises on the left similarly to the azygous vein and ascends adjacent to the vertebrae, draining the left renal vein, lumbar azygous vein, lumbar veins, and lower three posterior intercostal veins. It crosses the midline across the anterior surface of the eighth vertebral body and connects to the azygous vein on the right.

Interruption of the inferior vena cava with azygous continuation is usually present in patients with left atrial isomerism but may occur in situs solitus with a small remnant of inferior vena cava.[3] With congenital heart disease, the prevalence is approximately 0.6%.[26] Both the azygous and hemiazygous veins may be patent with azygous continuation.[3,27–29] Azygous continuation of the inferior vena cava has importance for patient care because cardiac catheterization may be more difficult in these patients. Patients with left atrial isomerism are prone to this anomaly and also prone

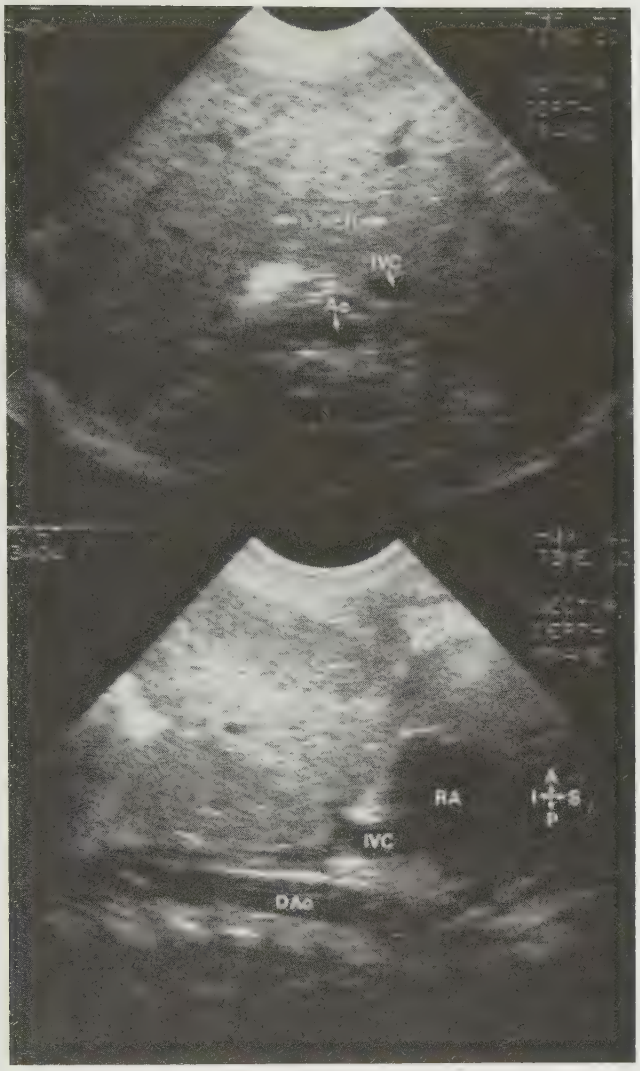

Fig. 84–11. Abnormal position of the inferior vena cava on the left in a patient with right atrial isomerism. Note that the aorta (Ao) and the inferior vena cava (IVC) run together. RA = right atrium; DAo = descending aorta.

to complete AV block. Such a patient may need an emergency pacemaker, which can be difficult to place via an azygous vein.

Hepatic Veins

Both hepatic lobes normally drain directly to the inferior vena cava. Partial and total anomalous connection refers to connection elsewhere of part or all of the hepatic veins. Partial hepatic connection directly to the heart is most common in right atrial isomerism but may occur in situs solitus or situs inversus.[3] Another reported site of partial anomalous connection is to the coronary sinus. Total anomalous hepatic venous connection occurs in left atrial isomerism, and the veins may connect to the heart via one trunk (most common) or two trunks. Anomalies of the hepatic veins can be diagnosed easily by echocardiography and may be important to identify before the correction of congenital heart defects or before liver transplantation.

MULTIPLE ANOMALIES

Complexes with multiple anomalies of systemic venous connection are almost invariably associated with abnormal atrial situs and atrioventricular septal defect (AV canal).[30–33] It is useful to screen for splenic presence by a blood smear for Howell-Jolly bodies in older infants and children with complex defects. The presence of abnormal stomach position, a midline liver, dextrocardia, azygous continuation of the inferior vena cava, bilateral bronchi or pulmonary arteries, or any abnormal venous connection other than a persistent left superior vena cava to the coronary sinus should raise suspicions of abnormal situs.

THE FUTURE: NEWER DIAGNOSTIC TECHNIQUES

Radionuclide studies can be used to detect abnormal shunting of blood into the left atrium. For example, left arm tracer injection will reveal early appearance of tracer in the left atrium in a patient with abnormal connection of a persistent left superior vena cava to the left atrium.[38,39] Nuclear magnetic resonance imaging techniques are proving to be sensitive in the diagnosis of venous abnormalities, especially with rapid acquisition flow display. Computed tomography may be useful in detecting abnormal thoracic venous structures.[40]

SURGICAL SIGNIFICANCE

The surgical significance of systemic venous anomalies lies in the need to plan for bypass cannulation technique[34] and to correct complex congenital heart defects. If systemic and pulmonary venous connections are near one another, then some type of baffle procedure may be necessary. If the operation is a type that is a variation of the Fontan procedure, then the ipsilateral superior vena cava and pulmonary artery may be connected with ligation of the superior vena cava as it meets the right atrium. Azygous continuation of the inferior vena cava will require a larger size of cannula at its site of connection because it is returning all of the inferior venous flow to the heart. Unroofed coronary sinus may be closed with a patch directly via the atrial septum or a left atrial incision.[35]

NONSURGICAL TREATMENT

If there is doubt about whether a persistent left superior vena cava can be ligated, then temporary balloon occlusion to the vein while measuring proximal pressure at catheterization can be used to test the outcome.[36] Obstruction of a superior vena cava after surgical repair of transposition of the great arteries has been successfully treated with balloon angioplasty at the time of cardiac catheterization.[3]

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CHAPTER 85

Arteriovenous Fistulae

L Paul Gerson

HISTORY

Perhaps the earliest report of an arteriovenous fistula was made by William Hunter in 1757.[1] In his paper, Hunter described a thrill and a bruit over the lesion and noted the presence of an enlarged artery proximal to the fistula. He pointed out that the thrill and bruit could be eliminated by exerting pressure over the feeding artery.

Sir Prescott Hewett in 1867 reported a congenital arteriovenous fistula in a 17-year-old girl who was born with enlargement of the right thigh, and, as the patient stated, "a peculiar beating" in the right leg.[2] Hewett described his patient as follows: "The right lower extremity was found to be much enlarged, being not only increased in circumference, but at least two inches longer than the left. The superficial veins were much dilated and stood out in the form of large, convoluted and tortuous cords under the skin. The femoral vein could also be felt to be much enlarged in the groin and in it could be perceived a distinct vibratory thrill. A very loud continuous blowing sound could be traced up the vein to the same spot."[2]

Reports of arteriovenous fistulae described the effects of these fistulae on heart size, blood pressure, skin temperature, and limb growth.[3–8] As these papers were published, a confusing array of names and descriptive terms for arteriovenous fistulae was compiled. At the same time, numerous syndromes were named that contained as part of their stigmata some sort of vascular malformation (Table 85–1).

In time, as the embryology of the vascular system was better understood, a unifying embryologic etiology for congenital vascular malformations was realized.[9–13] This concept has helped to replace the myriad of old terms with a more concise classification of arteriovenous fistulae. One special case—the coronary arteriovenous fistula—is discussed in Chapter 83 rather than here.

EMBRYOLOGY

The vascular system first appears within the primitive mesenchyme as undifferentiated blood containing spaces. These spaces coalesce, disappear by absorption, and separate from one another to form discrete channels that ultimately come to be the capillary

Table 85–1. Synonyms for Arteriovenous Fistula and Angioma Syndromes

Synonyms	
Cirsoid aneurysm	Strawberry birthmark
Racemose aneurysm	Nevus angiectoides
Pulsating angiomata	Port-wine mark
Hemangioma simplex	Angioma arteriole
Angioma telangiectaticum	Racemosum or plexiform
Hemangioma cavernosum	Serpentine aneurysm
Congenital arteriovenous aneurysm	
Angioma Syndromes	
Klippel-Trenaunay-Weber	Rendu-Osler-Weber
Parks-Weber	Blue rubber nevus
Sturge-Weber	Von Hippel-Lindau
Beckwith-Wiedemann	Maffucci
Kasabach-Merritt	Multiple neonatal hemangiomatoses

Table 85–2. Classification of Arteriovenous Fistulae

Designation	*Embryonic Stage at Time of Development*
Hemangioma	Capillary network stage
Microfistulous arteriovenous fistula	Retiform stage
Macrofistulous arteriovenous fistula	Retiform stage
Anomalous mature vascular channels	Stage of gross differentiation (arterial stem formation)

(From Szilagyi, D.E., Elliott, J.P., DeRusso, F.J., and Smith, R.F.: Peripheral congenital arteriovenous fistulas. Surgery, *57*:61, 1965.)

bed. Continued differentiation of the vascular bed results in the creation of separate venous and arterial conduits on either side of the capillaries. Arterial stems then make their way into the evolving vascular tree.

Woolard[14] has described this sequence of events as 1) the stage of undifferentiated capillary network, 2) the retiform stage, in which plexiform structures representing primitive arterial and venous channels evolve from the equipotential capillary bed, and 3) the stage of mature vascular stems following the disappearance of the primitive elements.

The development of the vascular system through this evolutionary process takes place from the fifth through the tenth weeks of fetal life.[15] Errors can occur at any step along the process and, depending on when the error occurs and which area of the vascular tree is involved, result in various types of vascular malformations.

CLASSIFICATION

Szilagyi et al.[16] created a classification of four types of congenital arteriovenous fistulae and correlated each with the stage of embryonic development during which the malformation was created (Table 85–2). They specifically noted that the lesion termed hemangioma did not represent a neoplasm, and that any growth these undergo is not from cell multiplication but from hemodynamic changes. In this classification, the microfistulous lesion was one that was not readily apparent angiographically, despite the fact that abnormal arteriovenous connections were present and could be detected by other means.

Malan and Puglionisi have devised a developmental classification that is primarily morphologic in its designation of the types of arteriovenous fistulae.[15] They proposed four types of congenital malformation based on where the defect occurs within the primitive vascular tree (Fig. 85–1).

While these classifications have helped to simplify and codify our understanding of arteriovenous fistulae, it should be borne in mind that not every case fits neatly into one category or another. In addition, methods of classification that depend heavily on inference about embryologic origin of malformations may become outdated and cumbersome when new embryologic evidence becomes available (as was learned with embryologic approaches to the nomenclature of intracardiac malformations). In actual practice, one encounters lesions that show elements of more than one type of vascular malformation, and the angiographer must be able to recognize and describe these components.

In this chapter the following morphologic classifications are used in discussion of the various types of arteriovenous fistulae (see Fig. 85–1):

1. Capillary angioma
2. Macrofistulous arteriovenous fistula
3. Truncal arteriovenous fistula

Capillary Angioma

Mulliken has demonstrated that some lesions of small vascular channels show the presence of endothelial cell proliferation and increased numbers of mast cells, indicating that these lesions are actually neoplasms.[17,18] We reserve the term *hemangioma* for these tumors. Thus, the term *capillary angioma* is used to describe congenital malformations of capillaries, to avoid any sense that these lesions are neoplasms (hemangiomas).

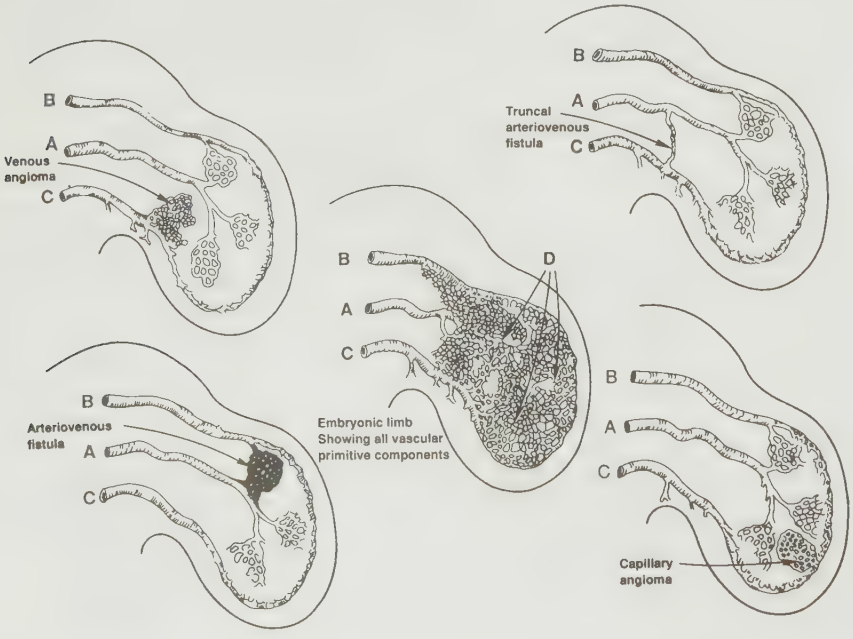

Fig. 85–1. Schematic representation of primitive vascularity and types of vascular malformations in the embryonic limb. A: axial artery; B: marginal cephalic vein; C: marginal caudal vein; D: primitive capillary network. (Adapted from Malan, E., and Puglionisi, A.: Congenital angiodysplasias of the extremities. J. Cardiovasc. Surg., 5:87, 1964.)

Capillary angiomas may be cutaneous or deep, flat or cavernous, single or multiple, or any combination of these possibilities. Cutaneous lesions usually present because of cosmetic complaints related to skin discoloration. The diagnosis is made by inspection of the lesion and by recognizing associated stigmata of syndromes that contain a capillary angioma as a constituent part.[19] Deep capillary angiomas usually present as a mass that has been present since birth. The natural history of these lesions varies. They may be static, they may grow larger because of hemodynamic change (not cell proliferation), or they may involute.[15,16,20,21]

Deep capillary angiomas within a limb are frequently associated with enlargement of that extremity. Parks and Weber termed this phenomenon *hemangiectatic hypertrophy*.[22] Vanderhoeft has shown that limb hypertrophy results from altered hemodynamics either by hyperemia or passive congestion. An increase in bone length is due to hyperfusion of the epiphyseal cartilage. Increased bone thickness is secondary to periosteal stimulation by increased blood flow.[23–25]

Microscopically, a capillary angioma is represented by large vascular cavities grouped in lobules or scattered in tissues. The wall is a single tract of endothelial elements, and capillary hemangiomas are considered huge capillaries, distended by altered hemodynamics.

Imaging studies of capillary angiomas have been carried out using angiography, ultrasonography, radionuclides, computed tomography (CT), and magnetic resonance imaging (MRI).[26–43] The goals of noninvasive imaging are 1) to detect the presence of a lesion; 2) to delineate accurately the extent and location of the abnormality and its relationship to adjacent structures; and 3) to uncover the underlying nature of the lesion.

An angioma is seen on CT scans as a well-circumscribed "soft tissue" density mass. Invasion of adjacent structures does not occur and is not consistent with the benign nature of this lesion. Calcifications, probably representing phleboliths, may be present.[26] The vascular nature of the lesion can be demonstrated with the use of contrast enhancement. The dynamic technique—a rapid series of images following a timed and measured bolus of contrast material—is particularly useful in demonstrating the hypervascularity of angiomatous masses. Benign neoplasms may be hypervascular as well, whereas malignant tumors are usually avascular or hypovascular.[27]

Magnetic resonance imaging may be the best noninvasive means for the study of a deep angioma. It produces images in the axial, sagittal, and coronal planes without using contrast material or ionizing radiation. On T_2 weighted images, the blood within an angioma produces a markedly higher signal than surrounding tissues, which allows for accurate identification of the extent of the lesion and understanding of its relationship to other structures.

Angiography may not yield complete delineation of a capillary angioma. One may note an increase in the number of arterial vessels in the region of the lesion. These branches are usually of small size. There may be no opacification of the draining veins, even if they are dilated (Fig. 85–2). Burrows et al.[44] have shown that vascular malformations may be differentiated from neoplastic hemangiomas angiographically. Hemangiomas show the presence of a well-circumscribed tissue stain usually arranged in a lobular pattern, which is not a feature of the capillary angioma type of vascular malformation (Figs. 85–3 and 85–4). Careful, selective angiography is still important in the evaluation of capillary angioma. One may discover the feeding vessels of the lesion, ascertain that a vascular lesion producing arteriovenous shunting is present, and add to the understanding of the underlying nature of the mass to plan therapy.

Macrofistulous Arteriovenous Fistula

Macrofistulous malformations encompass those vascular malformations made up of one or more feeding arteries joined to draining veins by an intervening tangle of ambiguous vascular channels. The walls of the intermediate channels may appear arterial, venous, or have features of both types of vessels, all of which contain oxygenated blood.[45–47] These anastomotic channels may be several millimeters in diameter and up to several centimeters long[47] (Figs. 85–5, 85–6, and 85–7).

Arteriovenous fistulae may occur anywhere within the body, although they are probably most common in the extremities (Table 85–3).[48,49] They usually present as a nontender swelling, associated with a thrill and bruit. In an extremity, dilated veins are usually present, and there is usually no change in skin pigmentation. The size of the extremity may vary; the limb may be normal, smaller, or larger than the opposite limb. Small size results from ischemia of tissues distal to the shunt.

Depending on the site of the lesion, presentation may be due to spontaneous hemorrhage or to alteration of physiologic function. For example, arteriovenous malformations of the gastrointestinal tract frequently present as bleeding. Lesions of the brain may manifest with headache, seizures, or hemorrhage. Arteriovenous malformations of the kidney may present with hypertension. Lesions in the extremities often present with claudication. Unlike acquired arteriovenous fistulae, congenital macrofistulous malformations do not usually produce systemic hemodynamic effects.[49]

Noninvasive imaging by ultrasound, CT, and MRI will demonstrate the presence of a vascular mass associated with arteriovenous shunting of blood. Magnetic resonance imaging is the method of choice for noninvasive imaging. T_2 weighted images show the relationship of the vascular malformation to adjacent soft tissue structures. T_1 weighted images are especially useful in showing the relationship of the malformation to adjacent bone. Further discussion of MRI can be found in Chapters 37 and 51. The depiction of the involvement of these structures is extremely helpful in planning therapy.[50]

Table 85–3. Arteriovenous Fistulae: 10-Year Experience at the Mayo Clinic[48]

	Congenital	*Acquired*
AV fistulae of the extremities	80	17
Aorta–inferior vena cava fistulae	0	7
Pulmonary AV fistulae	47	0
Renal AV fistulae	0	6
AV fistulae of the portal system	0	1
AV fistulae of the neck and face	11	4
Pelvic AV fistulae	1	5
AV fistulae of the chest wall	0	2
Total	139	42

(*Source:* Gomes, M.M.R., and Bernatz, P.E.: Arteriovenous fistulas: A review and ten year experience at the Mayo Clinic. Mayo Clin. Proc., *45*:81, 1970.)

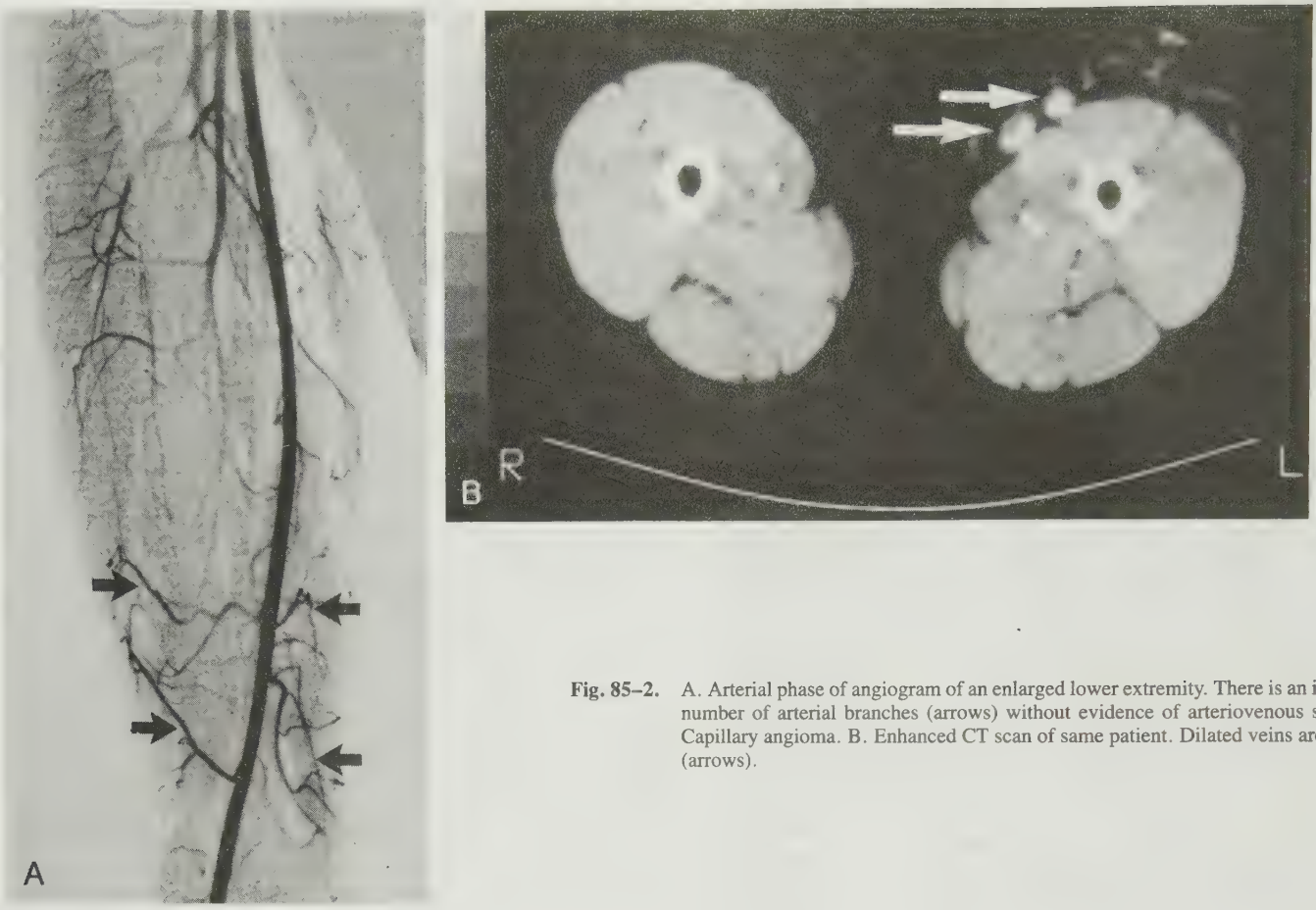

Fig. 85–2. A. Arterial phase of angiogram of an enlarged lower extremity. There is an increased number of arterial branches (arrows) without evidence of arteriovenous shunting. Capillary angioma. B. Enhanced CT scan of same patient. Dilated veins are evident (arrows).

Angiography of these lesions characteristically shows multiple, dilated, tortuous arterial feeders that enter a tangled mass of anastomotic vessels. Multiple dilated and tortuous draining veins appear almost immediately.

Views in multiple projections are usually required to deal with the considerable overlap of vessels. Subtraction of the films is useful, especially if the malformation is adjacent to bone. The flow through the lesion is rapid, and filming sequences should be at least two per second or faster. In unfolding the anatomy of a lesion, a helpful technique is to make serial subtractions. By this method a reverse film is made of each film in the series; this film is then used as a subtraction mask over the subsequent film. The resulting image shows what new vessels were opacified in that smaller unit of time. Digital subtraction angiography is advantageous because 1) it provides immediate subtracted images; 2) repeated studies in multiple projections can be rapidly obtained; and 3) dilute mixtures of contrast material can be used, thus conserving contrast dose and minimizing discomfort.

Truncal Arteriovenous Fistula

Truncal arteriovenous fistula results from abnormal communication of mature arteries and veins without an intervening anastomotic channel. A good example of this malformation is the "Vein of Galen Aneurysm." In many of these lesions the terminal ends of the anterior cerebral artery and branches of the posterior cerebral arteries join directly to the Vein of Galen, creating an enormous arteriovenous shunt. Other examples of truncal arteriovenous fistulas have been found between the vertebral artery and adjacent to the deep cervical vein, and between terminal branches of the external carotid arteries and the superior sagittal sinus. Large truncal fistulas are usually associated with neonatal congestive heart failure.

Angiographically, the lesions are seen as dilated arterial feeders that join directly to extremely dilated draining veins. The shunt is usually large and the circulation time shortened (Figs. 85–8 and 85–9).

Digital subtraction angiography is especially useful in these cases because one is often dealing with a small infant in congestive heart failure, which makes economy of contrast material an absolute requirement.

TREATMENT

In general, surgical cure of vascular malformations is impossible unless the lesion is simple or very well circumscribed.[51–53] Surgical difficulties have led to the development of nonsurgical modes of therapy, as well as a philosophy of conservative, watchful waiting.

Approximately 50% of deep capillary angiomas undergo spontaneous involution. There have been reports of the use of systemic steroids to bring an enlarging angioma under control.[54–57] The mechanism by which steroids affect vascular malformations is not

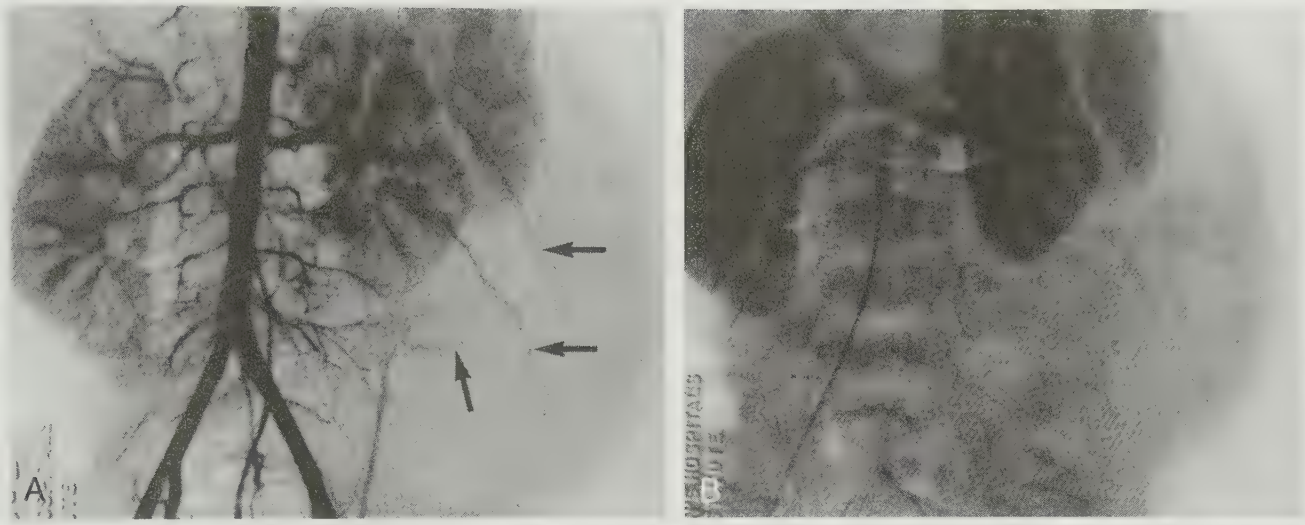

Fig. 85–3. A. Arterial phase angiogram of mass in left flank. Numerous arterial feeders (arrows) without early draining vein. Capillary angioma. B. Later phase shows diffuse, disorganized stain without evidence of any draining veins.

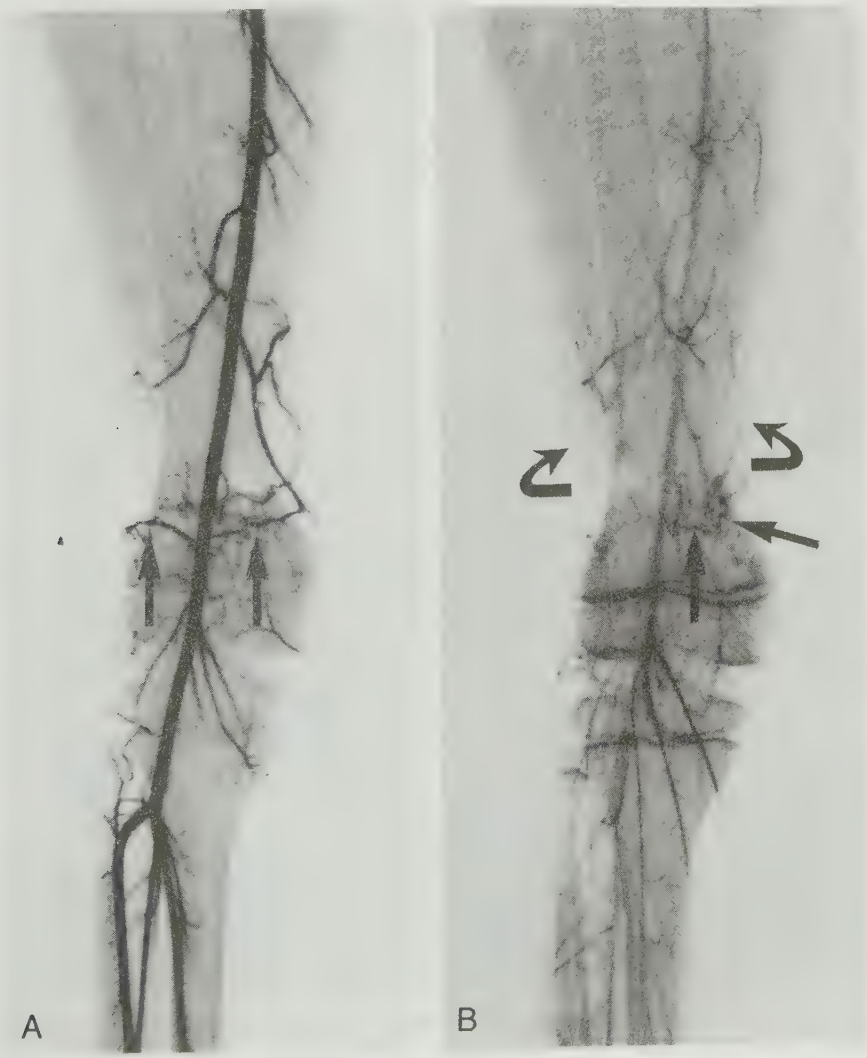

Fig. 85–4. A. Arterial phase of angiogram of enlarged lower extremity. Numerous, slightly dilated arterial vessels (arrows). No definite early draining vein. B. Later film shows early draining (curved arrows) and persistent stain in ambiguous connecting vessels (straight arrows). This is a capillary angioma with some macrofistulous characteristics.

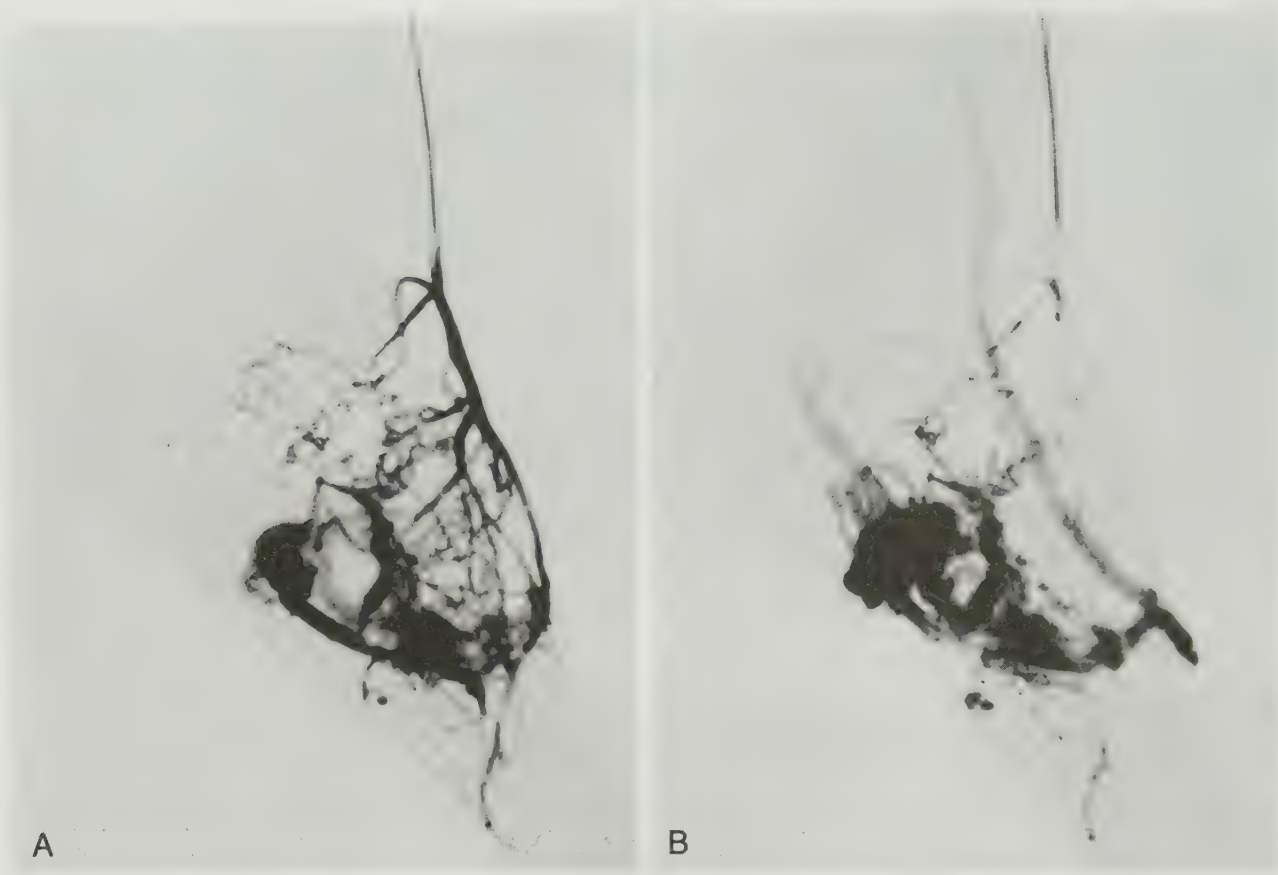

Fig. 85–5. A. Macrofistulous arteriovenous fistula of foot with numerous dilated feeding arteries. Immediate opacification of anastomotic channels and dilated draining veins. B. Venous phase showing densely opacified nidus and dilated draining veins.

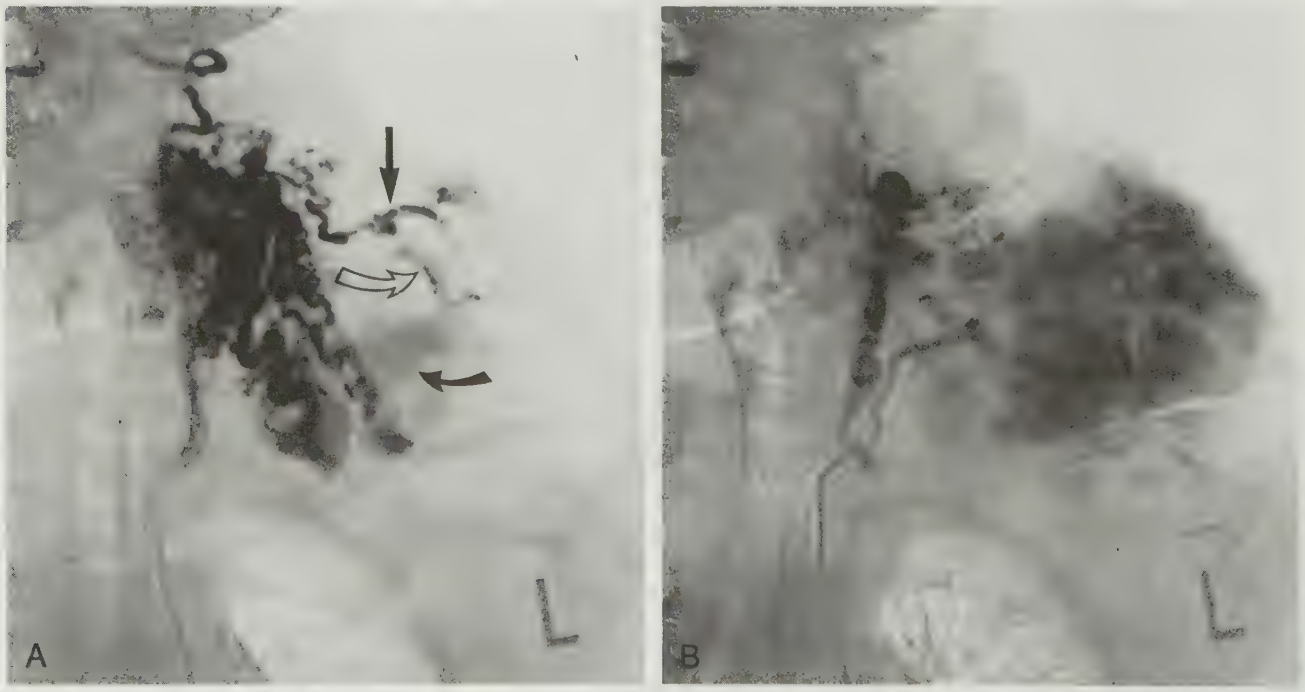

Fig. 85–6. (A) Macrofistulous lesion of neck, selective vertebral angiogram. Numerous dilated arterial feeders (solid arrow), immediate opacification of anastomotic channels (open arrow), and dilated veins (curved arrow). (B) Venous phase shows markedly dilated draining veins.

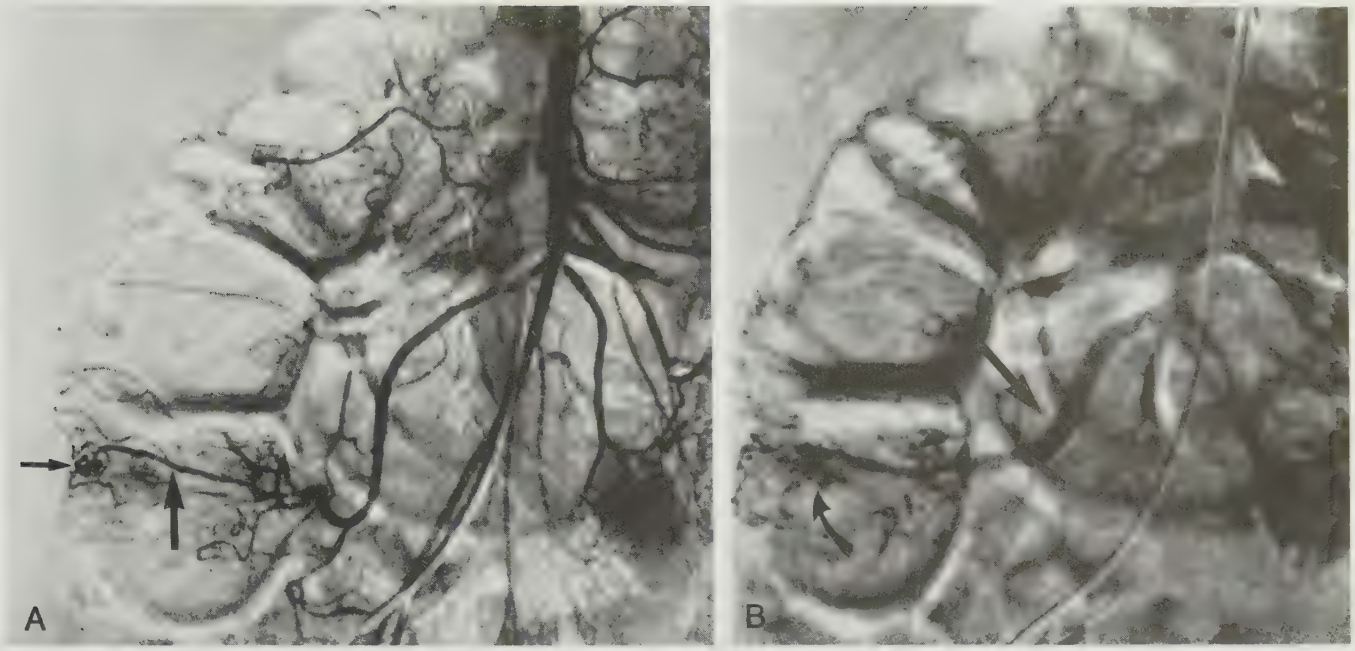

Fig. 85–7. (A) Arterial phase, selective superior mesenteric angiogram. Multiple dilated arterial vessels in cecum without immediate opacification of draining vein (arrow). (B) Venous phase shows dilated draining vein (arrows) and persistent stain in anastomotic vessels (curved arrows). This is a slow flow macrofistulous lesion.

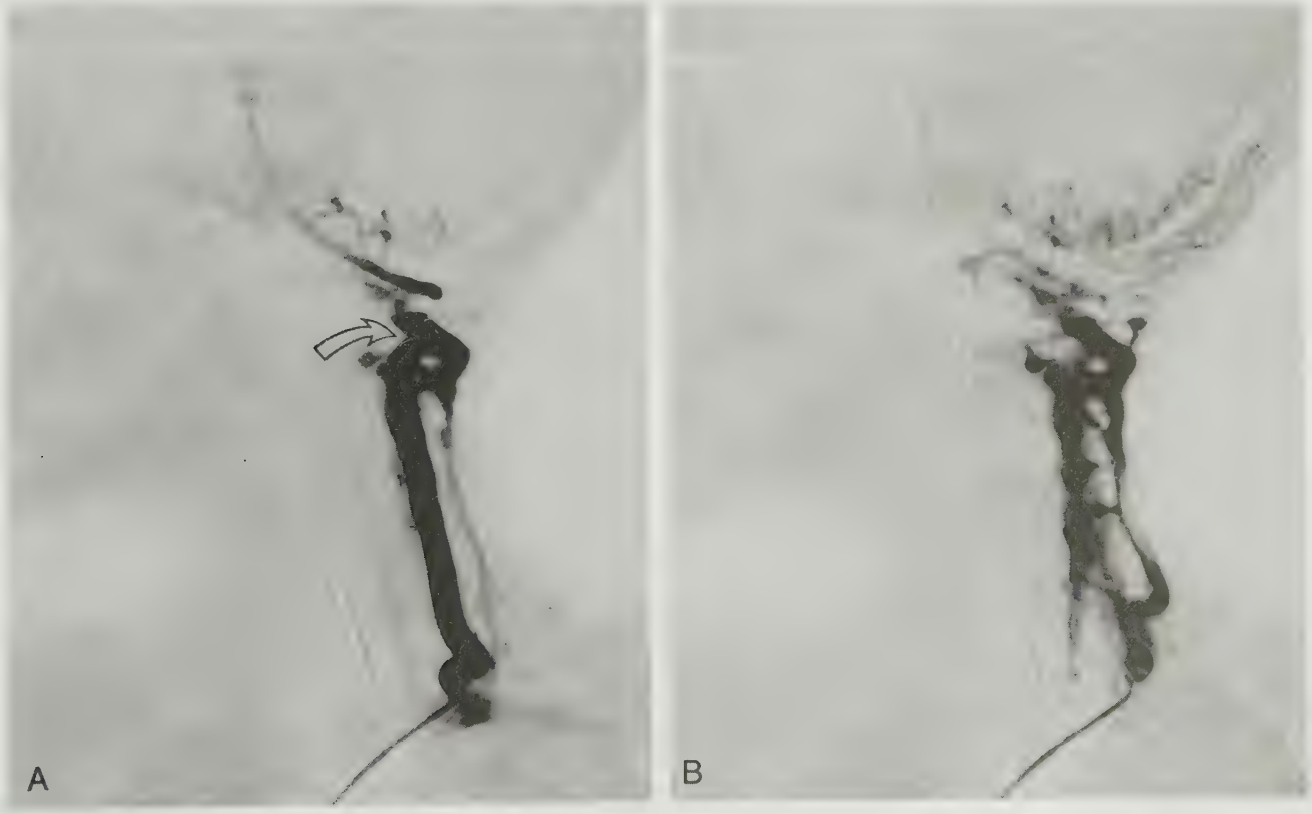

Fig. 85–8. (A) Truncal arteriovenous fistula. Selective vertebral injection shows dilated vertebral artery connected directly to enlarged cervical vein (arrow marks fistula). (B) Venous phase shows dilated venous plexus.

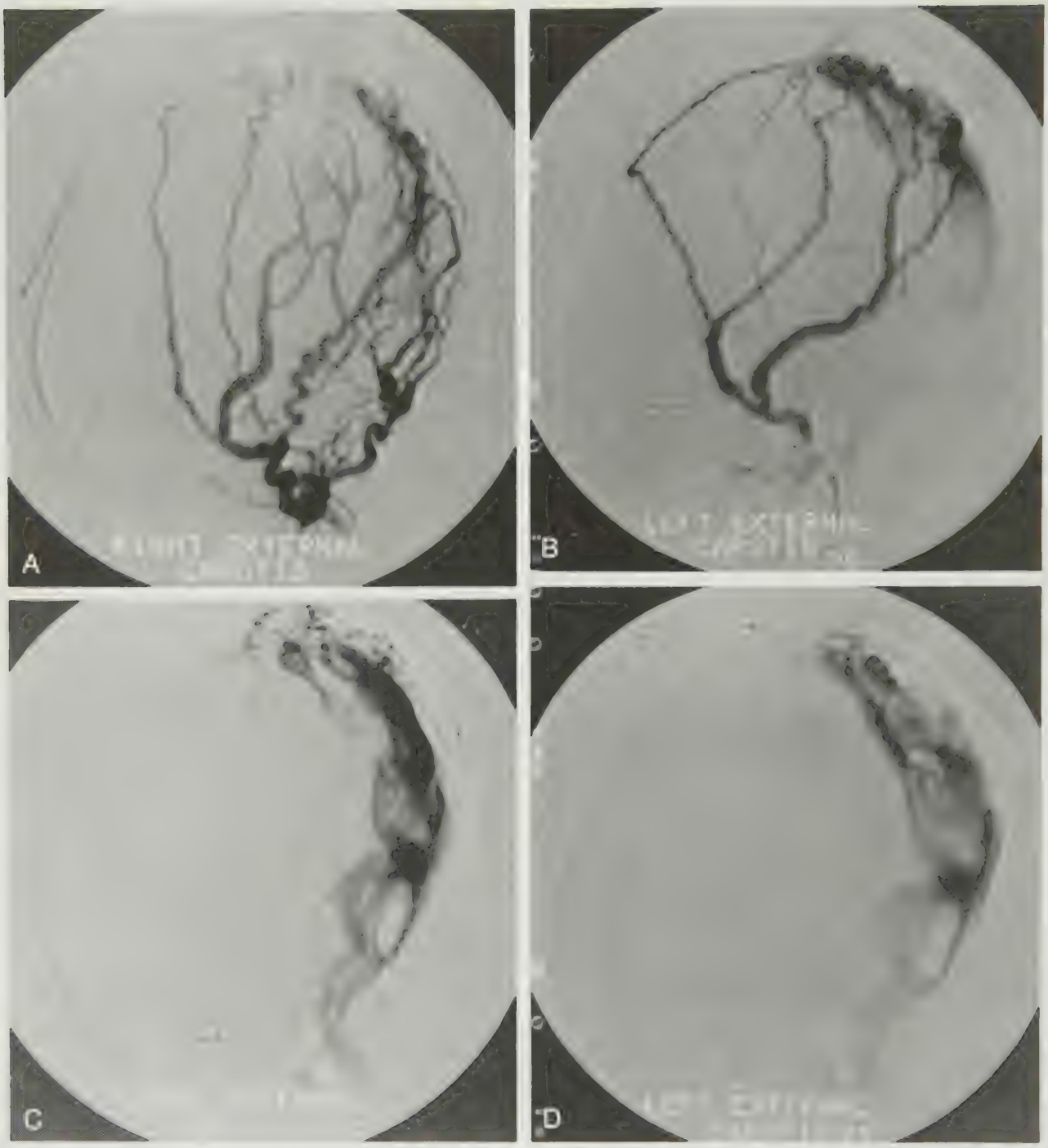

Fig. 85–9. Lateral views of right (A) and left (B) external carotid angiography show multiple dilated branches of both vessels. There are both truncal and macrofistulous connections between the external carotids and the superior sagittal sinus. (C and D) Venous phase shows some persistent opacification of anastomotic vessels and enormous dilation of superior sagittal sinus.

known. Hypotheses include alterations of endothelial cell metabolism and the incitement of precapillary arterial constriction.[56,57]

Transcatheter embolic therapy has emerged as a valuable method of treatment of vascular malformations. This method has several advantages. Percutaneous transcatheter treatment is less invasive than surgery and seeks to occlude the deep anastomotic channels that constitute the nidus of vascular malformation. Embolization can be used alone repeatedly as a palliative measure to reduce symptoms of a fistula or its interference with the function of an organ. Embolic therapy is also useful in combination with surgery or other forms of therapy.[58–71]

The aim of embolic therapy is to deliver the agent selectively to the vascular malformation as deeply into the lesion as possible without allowing escape of the embolus through the lesion into the venous outflow. In addition, one must make every attempt to deal with all the feeding arterial vessels. As with surgery, cure is not likely, and the therapeutic goal must be realistic. Effective palliation without adverse effect is a reasonable, attainable goal.

Numerous embolic or occlusive agents have been developed. The choice of material will depend on the location, type, and size of the malformation to be treated as well as on the experience of the physician. The longest lasting material that can be delivered as deeply and selectively as possible into the lesion, and which is most familiar to the surgeon, would be the ideal choice in each case.[72–77]

Embolic-occlusive agents fall into the following categories: 1) particulate; 2) liquid or semisolid; 3) detachable balloons; and 4) steel coil.

Particulate Agents

A large number of particulate agents exist[78–81] (Table 85–4). In general, they are readily available, nontoxic, and inexpensive. The longevity of thrombosis produced varies among the agents, ranging from several hours to permanent occlusion. The size of the particles also varies among the agents; some may be readily made into the appropriate size at the time of use.

Liquid and Semisolid Agents

Bucrylate (isobutyl 2-cyanoacrylate) is a member of the alkyl 2-cyanoacrylate family of adhesives. It is an advantageous agent for use in the treatment of arteriovenous fistulae.[82–85] The substance is liquid and low enough in viscosity to be injected through Nos. 2 and 3 French catheters, thus allowing highly selective embolization. The material can be made radio-opaque by mixing with Ethiodol or Pantopaque contrast material, and the polymerization time of the material can be controlled by its dilution with Pantopaque in a range from 1 to 8 seconds.[85] This agent has the advantages of high selectivity and permanence, without toxicity.

Table 85–4. Commonly Used Particulate Embolizing Agents

Agent	*Duration of Occlusion*
Autologous clot	Hours to days
Muscle	Days to weeks
Gelfoam	Weeks
Avitene	Weeks
Silastic, acrylic spheres	Permanent
Polyvinyl alcohol (Ivalon)	Permanent

At present, its use requires investigational exemption from the Food and Drug Administration.

Detachable Balloons

The use of detachable balloons for the embolization of arteriovenous malformations of the nervous system was introduced in Europe in the early 1970s. Since that time the materials and methods for this technique have undergone steady improvement. Balloon sizes range from 1 to 8 mm in diameter, and are placed in final position on a No. 2 French catheter advanced through a No. 5 French catheter, which is inserted through a No. 9 French introducer.[86–89] Once in place, the balloon is filled with radiopaque contrast material or silicone, then detached by tugging sharply on the No. 2 French catheter. The balloon should remain inflated indefinitely; its radiopacity will keep a record of its position. The disadvantage of this system is that the occlusion is made in the feeding vessels proximal to the deep anastomotic portion of the vascular malformation. The balloon thus exerts an effect somewhat like a surgical ligation. Balloons may be useful to block the larger vessels after the deep portion of the lesions have been dealt with using particles or bucrylate.

Steel Coils

Steel coils were developed by Anderson, Wallace, and Gianturco, and were first used in the late 1970s to occlude acquired arteriovenous fistulae.[90–92] The device consists of a stainless steel coil with strands of wool attached to promote thrombosis. The coils are supplied in straightened form in small holders. After satisfactory catheter position is obtained, the holder is placed through the stopcock and the coil is pushed through the catheter and out into the vessel with a guide wire. On emerging from the catheter, the coiled position is assumed in 3, 5, or 8 mm diameters, depending on the size coil used.

Like balloons, steel coils are useful to block the more proximal portions of feeding arteries but cannot reach deep arteriovenous communications in tangled macrofistulous arteriovenous fistulae. Their large size makes them useful for obliterating larger fistulae, particularly congenital truncal arteriovenous fistulae or acquired traumatic fistulae. Use of steel coils requires experience and expertise. It is wise to practice with them in vitro or in a laboratory setting before using them clinically.

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UNIT 5

INFLAMMATORY CARDIOVASCULAR DISEASE

CHAPTER 86

Acute Rheumatic Fever

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The importance of acute rheumatic fever (RF) and rheumatic heart disease (RHD) lies in its incidence, prevalence, mortality, disability, and cost to the community.[1]

Rheumatic fever is still the most common cause of heart disease in many developing countries. For example, in Egypt,[2] India,[3] and South America,[4] rheumatic heart disease is still the predominant form of heart disease in children. In the United States, although the prevalence is low and still decreasing in comparison to that in developing countries, rheumatic fever maintains its position as the leading cause of postnatally acquired heart disease in children.[5] An increase in prevalence in rheumatic fever has been reported in many areas of the United States, an eightfold increase in the annual incidence over the past decade being reported in the intermountain west.[6]

Rheumatic fever, which consists of delayed nonsuppurative sequelae of upper respiratory tract infection with group A beta-hemolytic streptococci, is a diffuse inflammatory disease of the connective tissue involving chiefly the heart, joints, brain, blood vessels, and subcutaneous tissue.[7]

"The term acute rheumatic fever today seems to be a misnomer, for it on occasion may be neither acute, rheumatic nor febrile."[7] Although the term emphasizes the involvement of the joints, the major importance of the disease comes from the involvement of the heart. In 1884, Lasegue described the fact that "rheumatic fever is a disease that licks the joints but bites the heart."

Recognition of the relationship between rheumatic fever and infection with group A beta-hemolytic streptococci has resulted in a clearer understanding of the epidemiology and natural history of the disease as well as in a more precise delineation of the clinical entity and practical approaches to its control.[7-9]

EVIDENCE THAT STREPTOCOCCUS IS THE INITIATIVE AGENT

The evidence that group A beta-hemolytic streptococcus is the sole initiative agent leading to RF and its recurrences is indirect. The organism cannot be recovered from RF lesions, and there is no satisfactory experimental model for the disease.

Epidemiological Evidence

Several epidemiological studies over many years have demonstrated sequential relationship between the outbreaks of streptococcal pharyngitis and rheumatic fever.[10] The several factors (environmental, host, and bacterial) that play a role in the development of RF are related to the incidence and severity of preceding streptococcal infections.

Immunological Evidence

Initial as well as recurrent attacks of RF do not occur without a streptococcal antibody response. The magnitude of the antibody response is also related to the attack rate of rheumatic fever and to recurrences following streptococcal pharyngitis.[11]

Clinical Evidence

Septic sore throat preceding acute rheumatic fever and its recurrences has been recognized clinically for over 100 years. It may be difficult to establish that streptococcal pharyngitis is the sole etiologic agent, since inconsistencies in this relationship have

been reported.[12,13] Rheumatic fever and its recurrences may occur without recognizable preceding sore throat.

Prophylactic Evidence

Convincing evidence is provided by the prevention of both initial and recurrent attacks of rheumatic fever by penicillin therapy.[11]

STREPTOCOCCUS: THE INITIATING AGENT

Streptococci are a group of gram-positive microorganisms that are widely prevalent in nature. They are spherical or oval in shape. When cultured, they are arranged in chains. Some are members of normal human flora. Others are associated with important human diseases caused by infection or sensitization by streptococci.

The streptococcus (Fig. 86–1) is composed of a core of cytoplasm surrounded by a cytoplasmic membrane and a cell wall. The cell wall, in turn, is surrounded by a capsule that constitutes the external surface of the organism.

The ability of streptococci to hemolyze red cells to varying degrees is one basis for their classification. Alpha-hemolytic streptococci form colonies surrounded by an ill-defined greenish halo in which hemolysis is incomplete. Beta-hemolytic streptococci produce a clear zone of complete hemolysis on blood agar. These must be carefully differentiated from other hemolytic species such as other streptococci and gram-negative organisms by colony characteristics and Gram stain. Gamma streptococci do not have any effect on blood-containing media.

Beta-hemolytic streptococci were classified into several groups by Lancefield, who labeled them alphabetically according to a polysaccharide antigen in the carbohydrate layer of the cell wall. Group A streptococci have also been called Streptococcus pyogenes. This group of streptococci is responsible for over 90% of human streptococcal infections and inflammatory syndromes, among which are acute rheumatic fever and acute glomerulonephritis. The group A carbohydrate moiety of the cell wall has been shown to be antigenically similar to glycoproteins of bovine and human cardiac valves.[14] This relationship has led to speculation about a role for this cell wall component in the pathogenesis of valvular damage in rheumatic fever.

Beta-hemolytic streptococci of groups C, G, and B are carried persistently in the throats of some people. These groups may cause unnecessary concern when isolated from throat cultures if the identity of the group is not determined.[7]

The biology of the group A streptococcus cannot be understood without a thorough knowledge of the structure of its cytoplasmic membrane, cell wall, and external capsule. Many recent studies have paid great attention to this last feature.[15–17] The capsule, which is the outermost part of the cell, is formed of hyaluronate. It is nonantigenic and chemically indistinguishable from hyaluronic acid of humans and other mammals. Hyaluronate is antiphagocytic but is of doubtful significance in human infections because most normal human sera contain a factor that neutralizes its effect.[18]

The other protein layers and their fimbriae are attached to the surface of the organisms and contain the M-protein and lipoteichoic

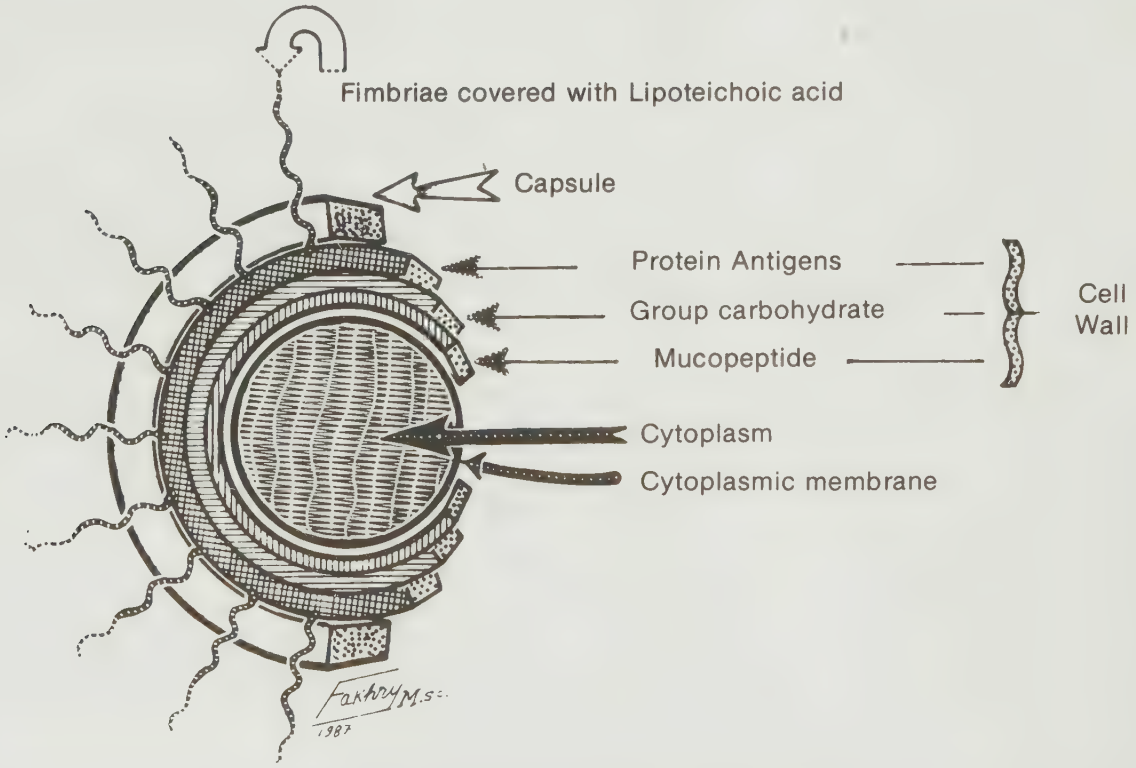

Fig. 86–1. Schematic diagram showing the structure of the streptococcal cell wall. The fimbriae covered with lipoteichoic acid help the organism to adhere to the throat epithelium (adherence factor). These fimbriae, being projections from the protein layer of the cell wall, contain M-protein, the virulence factor. Each of the different layers of the cell wall and the cytoplasmic membrane have been shown to cross-react with different antigens from different structures of the mammalian heart, including the human heart.

acid. The M-protein provides the streptococcal cell antiphagocytic properties. It is a primary virulence factor and induces the formation of type-specific antibodies, which are the basis of type-specific immunity. M-protein is a coiled molecule (double alpha-helix) with striking physicochemical similarity to mammalian tropomyosin.[19] Evidence has been presented that a protein closely associated with the M-protein cross-reacts antigenically with an antigen in heart muscle.[20] Other proteins, T and R, may be associated with the M-protein. Immunity to virulent strains of group A streptococci is related to the production of antibodies to the specific M-protein.[21] Such antibodies persist for many years following pharyngeal infections. Should these antibodies disappear from the circulation with time, they can be quickly recalled by minor antigenic stimuli.[22] So it appears that the type specific immunity is lifelong and that reinfection with the same type of group A streptococcus is extremely rare. Group A streptococci become vulnerable to phagocytosis once they have been exposed to their specific anti-M antibody, and they are rapidly destroyed by human blood phagocytes. As children approach adolescence, streptococcal throat infections become less frequent, whereas immediate and delayed skin allergy to streptococcal products becomes increasingly severe. The multiplicity of M-type group A streptococci and allergic reactions to epitopes of M-proteins are among the reasons why an effective vaccine has not been produced to date.[7]

The mucopeptide innermost layer of the cell wall is responsible for the shape of the cell. The cytoplasmic membrane is an antigenic lipoprotein, which cross-reacts with several mammalian tissue antigens, including glomerular basement membrane and sarcolemmal antigen.

Cross-reacting antibodies occur because of molecular mimic between the human host and the cell wall of the streptococcus and the cytoplasmic membrane.[23] Autoantibodies have been shown in sera of patients with RF to cardiac, skeletal, and smooth muscles, heart valve fibroblasts, neurons in basal ganglia, some determinants of connective tissue, thymus, and lymphocytes.[24] Such antibodies were detected in higher titres in RF patients than in patients with uncomplicated streptococcal infections. M-serotypes 5, 6, and 19 show cross-reactive immunity with cardiac myosin.[25]

The streptococcal fimbriae also contain lipoteichoic acid, which is essential for the organism's adherence to the epithelial cells of the oral mucosa[26] and respiratory tract.

In addition to the cell wall antigens described, there are many extracellular products that are elaborated by group A streptococci. These products have a wide variety of biological properties. Some of these products are sensitizing agents, some are cytotoxic, some are enzymes, some are toxins, and some have structural similarity to human host tissues.

Among the *sensitizing substances* is a non-type-specific protein antigen associated with M-protein,[23] which has been considered responsible for the delayed hypersensitivity of humans to M-antigen vaccines. In addition, streptolysin O has been shown to cause anaphylactic reactions in previously sensitized animals.

Cytotoxic substances include streptolysin O, which causes cytolysis of erythrocytes and has a severe cardiotoxic effect on rabbit, rat, and guinea pig hearts. The pathology is inhibited to a great extent by skin lipids. This might explain the absence of rheumatic fever after skin infections.[27] Erythrogenic toxin causes the rash characteristic of scarlet fever. Erythrogenic toxin is also antigenic, giving rise to the formation of specific antitoxins.

Several enzymes are produced by the streptococci. They are not type-specific. All, with the exception of streptolysin S, are antigenic. Antibodies to these enzymes can be measured in blood and are used to diagnose recent streptococcal infection.

Hemolysins (Streptolysins)

Streptolysin O, which is active only in the reduced state, is rapidly inactivated when oxidized. It elicits formation of antistreptolysin O, which blocks hemolysis by this antigen. High levels of antistreptolysin O (in excess of 160 to 200 Todd units) are considered abnormal and suggest either recent infection with streptococci or persistently high antibody level following an earlier exposure in a hypersensitive person.

Streptolysin S is an oxygen-stable product that causes hemolysis on blood agar. It is not antigenic.

Streptokinase (Fibrinolysin)

Streptokinase transforms the plasminogen of human serum to plasmin, an active proteolytic enzyme that digests fibrin and alters proteins. Streptokinase can elicit the formation of antistreptokinase.

Hyaluronidase

Hyaluronidase is an enzyme that splits hyaluronic acid, an important component of the ground substance of connective tissue, thereby aiding in the spread of infection (spreading factor). Hyaluronidase elicits formation of antihyaluronidase.

Deoxyribonucleases

There are four deoxyribonucleases (A, B, C, and D), all of which are antigenic. Deoxyribonuclease B, also known as streptodornase, is produced in the largest quantities in response to group A streptococcal infections and is the most consistently found deoxyribonuclease.

Diphosphopyridine Nucleotidase

This enzyme is related to the ability of the organisms to kill leukocytes.

Streptococcal Esterase

A rise of antistreptococcal esterase occasionally occurs without a rise of antistreptolysin O in hemolytic streptococcal infections.[28,29]

EPIDEMIOLOGY OF THE STREPTOCOCCUS AND RHEUMATIC FEVER

Many of the epidemiologic features of RF can be explained by the epidemiology of streptococcal infections of the upper respiratory tract.[30] Crowding from inadequate housing is probably the main risk factor in acquiring streptococcal infections and resulting rheumatic fever. The high incidence of streptococcal respiratory infections in the winter and spring probably accounts for the frequency of onset of rheumatic fever in these seasons.[31]

Since Halsey's study in 1921,[32] those who investigate rheumatic fever have been impressed with the diminishing frequency of the disease, particularly in the relatively affluent populations of North America and Europe. Reasons for this decline have been uncertain. Antibiotics for the treatment and prevention of streptococcal in-

fections are likely to have been a factor; however, the incidence and death rate from the disease were decreasing before the introduction of antibiotics. Improved social conditions such as better housing seem likely to have contributed to the decline.

The prevalence of rheumatic heart disease among U.S. schoolchildren has dropped sharply in recent years.[5] However, rheumatic heart disease still constitutes the leading cause of death from heart disease in young people in most parts of the world and continues to be a serious public health problem.[33] The resurgence of rheumatic fever as a clinical problem for pediatric cardiologists in some areas of the United States has been emphasized.

The following are some of the factors that might affect the attack rate of rheumatic fever.

HOST FACTORS

Age, Sex, and Race

Acute rheumatic fever occurs most commonly in the young school-age child and very rarely in infancy. No true differences in sex, race, or ethnic group susceptibility have been established. Living conditions seem to account for apparent increases in susceptibility.

Genetic Predisposition

As early as 1889, Cheadle observed that rheumatic fever can occur in more than one member of the family.[34] Since then, many reports have confirmed familial incidence. Some reports even concluded that susceptibility to rheumatic fever is caused by a single autosomal recessive gene. However, studies of siblings and twins, both monozygotic and dizygotic, have failed to confirm this.[35] The high familial incidence has largely been attributed to the family's standard of living, which has favored a spread of streptococcal infections to more than one member.[36,37] Recently, Ayoub and associates showed findings to support the concept of genetically determined susceptibility to rheumatic fever and particularly to rheumatic heart disease.[38] Their findings could be ascribed to a disease-associated immune-response gene. Two B-lymphocyte alloantigens have also been identified by monoclonal antibodies in the sera of patients with well-documented rheumatic fever in the past. These two antibodies identified approximately 92% of all rheumatic fever patients and suggested the presence of a genetic marker for susceptibility to rheumatic fever.[39]

STRAIN OF STREPTOCOCCI

Although groups C and G streptococci can cause pharyngitis and might provoke an immune response, only group A streptococcal infections of the upper respiratory tract result in rheumatic fever.

It is well recognized that a relatively small number of M types are the most common and dangerous rheumatogenic pharyngeal strains, while others may be nephritogenic. Studies in Memphis have shown seasonal epidemiological separation of acute rheumatic fever from acute glomerulonephritis.[40] Populations in the southern United States in which pyoderma and rheumatic fever both occur show a large number of acute glomerulonephritis cases with virtually absent rheumatic fever in the summer when streptococcal pyoderma is prevalent. In the fall when school begins, acute glomerulonephritis and pyoderma decline rapidly, and acute rheumatic fever appears abruptly. In Trinidad, where both acute glomerulonephritis and acute rheumatic fever are concurrent in the same population with little seasonal variation, cyclical epidemics of acute glomerulonephritis have been repeated[41] but without parallel changes in the incidence of rheumatic fever. A study of streptococcal strains in this population showed a clear distinction between the serotypes associated with glomerulonephritis and those associated with rheumatic fever.[42]

Variations in the rheumatogenicity of group A streptococcal strains may be a factor influencing the attack rate of rheumatic fever. A decline in rheumatic fever has been associated with the decline in prevalence of several of the major M serotype streptococci that are notorious for causing epidemic rheumatic fever (for example, types 5, 14, and 24).[43]

ROUTE OF INFECTION

The necessity for the preceding streptococcal infection to occur in the throat or upper respiratory tract rather than skin is well documented.[44] Several hypotheses have been offered. The possible role of lymphatic connections between the pharynx and the heart has been considered. The embryological derivation of the heart links it with the neck's vascular, lymphatic, and nerve supply. Connection between the tonsils and the heart in human beings has been demonstrated by injection of lymphatic channels in cadavers.[45] The difference in the sites of infection could be the result of a difference in the strains that are commonly pathogenic at these two sites. The feeble antistreptolysin O response with streptococcal infections of the skin[44] and demonstration of skin lipids that inhibit the biological effects of antigenicity of streptococcal enzymes[46] might also explain why rheumatic fever does not occur after streptococcal impetigo. It has been speculated that the streptococcal strains associated with rheumatic fever adhere more avidly to pharyngeal cells of the patients who are susceptible to develop acute rheumatic fever than do strains that are not associated with rheumatic fever.[47]

SEVERITY OF STREPTOCOCCAL INFECTION AND IMMUNE RESPONSE

Antibodies to streptococcal antigens are consistently more elevated in patients with rheumatic fever than in patients who have uncomplicated streptococcal pharyngitis.[48] The rheumatic host might be hyperimmune because of more frequent or more severe streptococcal infections.

Rheumatic fever followed at a fairly predictable attack rate (approximately 3%) in epidemics of frank exudative streptococcal pharyngitis caused by virulent group A streptococci in military populations[30] regardless of age, race, or ethnic group. The most important major predictor of the occurrence of rheumatic fever in these epidemiological studies was the magnitude of the immune response to the antecedent streptococcal infection.[49]

THEORIES ON HOW STREPTOCOCCAL INFECTION CAUSES RHEUMATIC FEVER

Acute rheumatic fever results from the interaction of three main factors: an etiological agent that is the group A beta-hemolytic

streptococcus; an organ site dependence; and a vulnerable host because rheumatic fever occurs only in a small percentage of patients infected with group A beta-hemolytic infections (Fig. 86–2).

Although it is clear that rheumatic fever follows group A streptococcal infection of the upper respiratory tract, how the organism causes rheumatic fever is still unclear.[7] Many theories have been postulated, but none explains the whole story. The difficulties arise because of the inability to definitely relate any known component or product of group A streptococci to rheumatic fever and because of the failure to provide a favorable hypothesis that encompasses all possible factors contributed by the organism as well as the host.[45,50]

So far, there has been no conclusive evidence that rheumatic fever results from persistence of streptococci either in their original or L-forms.[51]

The concept that rheumatic fever is a hypersensitivity reaction was drawn from the analogy of rheumatic fever to serum sickness, including its latent period. The rarity of rheumatic fever among infants suggests that one must experience repeated streptococcal infections to develop sufficient hypersensitivity for rheumatic fever to occur.[52] However, type-specific antibody data from several laboratories indicated that rheumatic patients did not have more frequent streptococcal infections before their first attack.[53] The infrequency of rheumatic fever in infants could also be explained by the rarity of streptococcal infections in this age group.

Much interest has been shown in the possible role of cell-mediated cytotoxic reactions to various streptococcal antigens. Delayed hypersensitivity skin tests to streptococci and their products are generally more intense in rheumatic subjects than in nonrheumatic controls and are particularly intense with extracts of hemolytic streptococci compared with nonhemolytic streptococcal strains.[54] Read and associates[55] showed that patients with acute rheumatic fever have inhibition of migration of leukocytes to group A streptococcal membrane antigens. Patients with uncomplicated streptococcal infections with high antistreptolysin O titers react to these antigens in a normal fashion. This cellular reactivity proved to be specific for group A streptococcal membranes. Group C and D streptococcal membranes elicited normal responses in both rheumatic and nonrheumatic subjects. Sorour and his associates[56] demonstrated significantly increased active T-rosette enhancement to streptococcal antigens among established rheumatic patients as compared with nonrheumatic subjects. Data indicating significant alterations in both helper and suppressor T-cell types in the peripheral blood of children with acute rheumatic fever have been shown to return to normal after recovery.[53,57]

The most popular theory of pathogenesis is that rheumatic fever results from some type of autoimmunity. Numerous reports have shown that the serum of patients with rheumatic fever contains antibodies to heart tissues. These antiheart antibodies are gamma globulins with specificity for cardiac components reacting primarily with the sarcolemma. Their binding is also associated with deposition of large amounts of C_3. Antiheart antibodies occur more frequently in rheumatic fever patients who develop carditis. Massive deposits of gamma globulins have also been identified in the hearts of children who died of rheumatic carditis. Pericardial tissue has shown extensive deposition of IgG, IgM, and C_3, a finding suggesting an immune mechanism for the pericarditis of acute rheumatic fever.[58] Kaplan and associates, as well as several more recent reports, have demonstrated that rabbit antisera against certain group A streptococci react with human heart preparations,[59,60] indicating cross-reaction between the streptococcus and human heart. Cardiac damage by trauma or ischemia results in biochemical changes manifested by the production of autoantibodies.[60] This raises the question: Is the antiheart antibody in rheumatic carditis the result or the cause of tissue injury? Antibodies to other tissues have been found in the sera of patients with rheumatic fever. A 95% incidence of smooth muscle antibody was found in sera from 55 rheumatic fever patients compared to 12% from overall hospital patients.[61]

To summarize (Fig. 86–2), one can conclude that for acute rheumatic fever to occur, a certain strain of group A beta-hemolytic

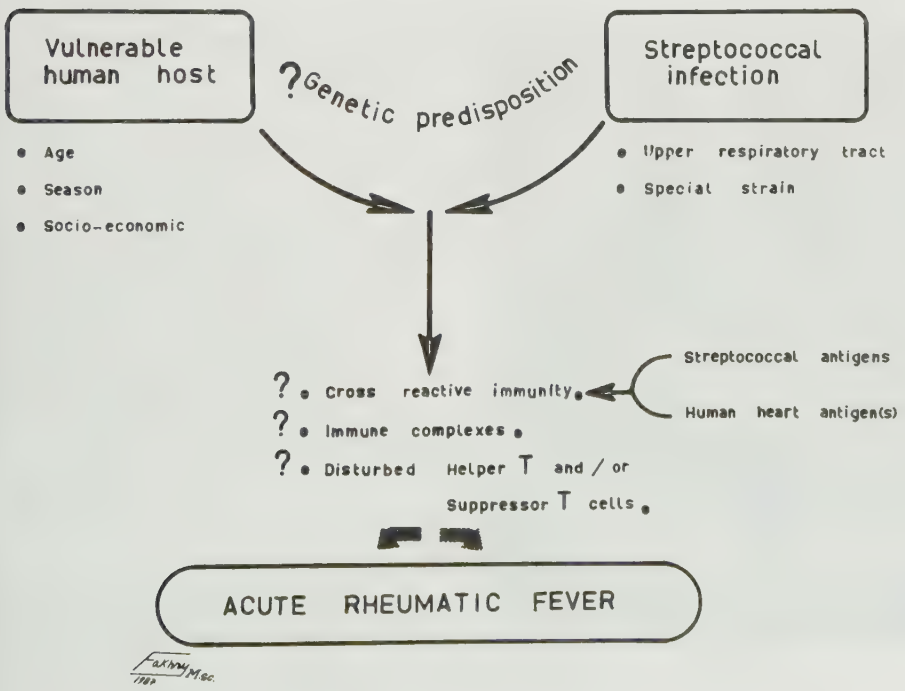

Fig. 86–2. Diagram showing the factors leading to rheumatic fever. The question marks show the as yet rather obscure factors that are possibly related to the complex pathogenesis of rheumatic fever.

streptococcus must infect the upper respiratory tract of a vulnerable host. Age, season, and socioeconomic standards are responsible for the frequency and spread of such streptococcal infections. The possible genetic predisposition to be afflicted with rheumatic fever, added to the above, creates the perfect human host. The molecular mimicry between certain parts of the streptococcus and tissues of the host may lead to cross-reactive immunity, in which the immune system will damage both the streptococci and certain tissues of the patient, especially the heart. This, together with the disturbed helper and suppressor T-cells, may bring about a "final blow" and lead to the complex immune system disturbance that results in acute rheumatic fever and its sequelae of cardiac damage.

PATHOLOGY OF RHEUMATIC FEVER

Rheumatic fever is characterized pathologically by two main lesions in the connective tissues occurring particularly around small blood vessels.

The first and the earliest lesion is exudative, degenerative, and inflammatory. This consists of edema of the ground substance and fragmentation of collagen fibers. There is cellular infiltration by T-lymphocytes, macrophages, B-lymphocytes, and mast cells. Scattered deposits of eosinophilic granular material (fibrinoid) occur in the ground substance. This exudative-degenerative inflammatory lesion contributes to transitory manifestations of rheumatic fever and responds to anti-inflammatory agents. This early phase lasts two to three weeks and is followed by the second lesion.

The second characteristic lesion of rheumatic fever is a proliferative one that may persist for many months or years.[62] The characteristic proliferative lesion is the Aschoff's nodule. The proliferative lesion probably does not respond to the anti-inflammatory agents. The myocardial Aschoff's nodule (Fig. 86–3) is usually oval in shape. There is a paravascular aggregation of large multinucleated cells in a basophilic cytoplasm. Many of these cells have a characteristic owl-eye nucleus. There usually are rosettes around an avascular core of fibrinoid or necrotic protoplasm.

The Aschoff's nodule, from its description in 1904, was thought to arise from connective tissue until Murphy challenged this traditional concept in 1960[63] and postulated that it resulted from injury to the cardiac muscle fibers. Three years later, Wedum and McGuire[64] suggested that the Aschoff's nodule is from neither connective tissue nor cardiac muscle but is formed because of injury to the endothelium of cardiac lymphatics that leads to blockage of the lymphatics. In 1973, Hutchins and Paige[65] suggested that Aschoff's nodules might be derived from nervous tissue, since they noticed that the Aschoff's cells resembled the Schwann cells of normal cardiac nerve fibers and that Aschoff's nodules are formed at the termination of small nerves.

Not only is the origin of Aschoff's nodules controversial, but the functional impact of nodules on the heart and relation to the course and severity of rheumatic attacks are not clear.[63,66] The persistence of Aschoff's nodules for many years after a rheumatic attack is well documented. Biopsies of left atrial appendages obtained during mitral valve surgery for mitral stenosis have demonstrated the persistence of Aschoff's nodules in patients who no longer have clinical or laboratory evidence of rheumatic activity or recent streptococcal infection.[67] The persistence of Aschoff's nodules might be related to progressive fibrosis and stenosis of the mitral valve.

The three layers of the heart may be involved, leading to what is known as "rheumatic pancarditis."

Pericarditis

Rheumatic pericarditis consists of a serofibrinous pericarditis with effusion. The pericardium has a characteristic shaggy appearance caused by deposition of fibrin on its surface (Fig. 86–4). With healing, fibrosis and adhesions develop that may partially or completely obliterate the pericardial space. Constriction does not occur.

Myocarditis

The myocardium is affected not only by Aschoff's nodules but also by interstitial inflammation and myocardial cell damage. In-

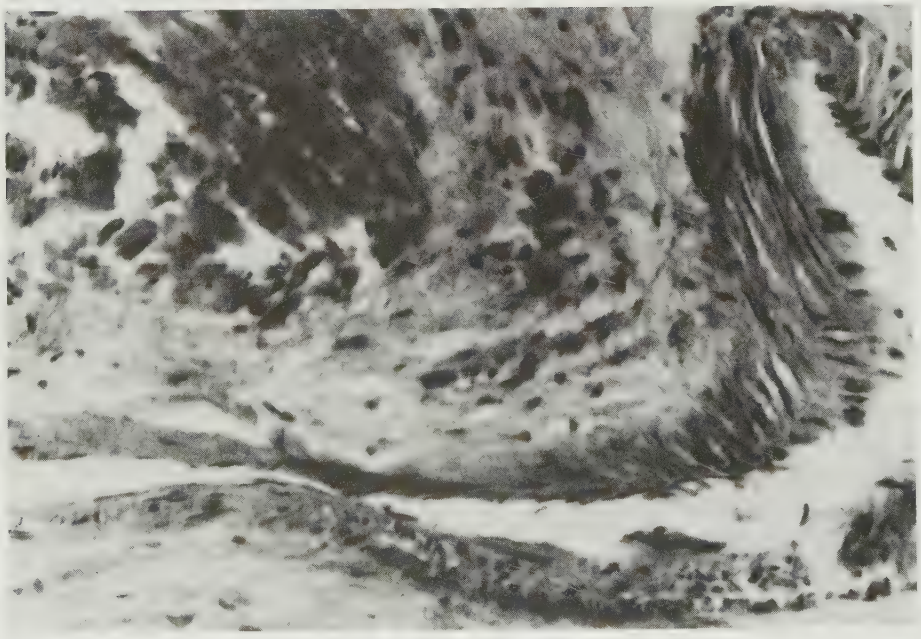

Fig. 86–3. A paravascular Aschoff's nodule (center of photomicrograph) showing a central area of fibrinoid change and an Aschoff's giant cell surrounded by an edematous intermyocardial connective tissue. (Courtesy of S. Mahfouz, M.D., Pathology Department, Cairo University.)

Fig. 86–4. Unopened heart showing a shaggy, rough, opaque pericardium that is characteristic of rheumatic fibrous pericarditis. Part of the pericardium has been removed showing unremarkable gross changes in the underlying cardiac muscle. (Courtesy of S. Mahfouz, M.D., Pathology Department, Cairo University.)

terstitial myocarditis may be an important factor in the pathogenesis of heart failure during rheumatic activity. This myocarditis is found mainly in the vicinity of the Aschoff's nodules and around blood vessels[68,69] with loss of striations, fatty degeneration, and vacuolation of myocardial cells. Myocytolysis and complete loss of fibers may be seen in some areas.[63]

Endocarditis

Endocarditis affects the mitral and aortic valves and, rarely, the tricuspid or pulmonary valves. In the active phase, the valves become edematous. Endocardial surfaces are damaged along the contact margins 2 or 3 mm from the free edges. At this site, tiny vegetations are formed that consist of platelet thrombi (Fig. 86–5). When inflammation subsides, fibrosis with vascularization and contracture of the leaflets follows. Similar changes affect the chordae tendineae and the annulus. The site of damage at contact points of the cusps suggests that trauma determines the position of the damage. Valve trauma also determines the frequency with which the various valves are involved. The mitral valve, closing at the highest pressure, is subjected to the greatest stress and is therefore the most frequently affected. If inflammation is severe, damage of cusps occurs with development of insufficiency. With milder inflammation, thickening and adhesions take place between the cusps. Adhesions gradually increase with development of stenosis of the valve orifice.

The Conduction System

The high frequency of prolonged P-R interval in acute rheumatic fever is not reflected in pathological changes in the atrioventricular node or bundle of His.[70] The evanescence of atrioventricular block and its reversibility by atropine suggest a functional rather than a structural lesion.

Arteritis of the Coronary Arteries and Other Arteries

The coronary arteries have been well described in rheumatic fever.[70] Coronary arteritis is considered by some to be important

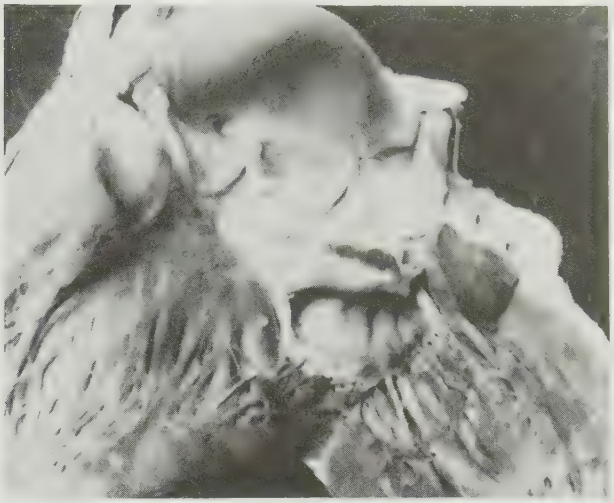

Fig. 86–5. Opened left ventricle displaying both the mitral and aortic valves of a patient with acute rheumatic fever. The mitral valve shows small (1–2 mm) brown, linear vegetations situated on the atrial surface of both anterior and posterior mitral leaflet margins. The aortic valve is grossly unaffected. (Courtesy of S. Mahfouz, M.D., Pathology Department, Cairo University.)

in producing the myocardial damage in rheumatic fever. However, thrombosis of large coronary vessels is very rare.

EXTRACARDIAC PATHOLOGY

Joints

In rheumatic fever there is inflammation, swelling, and edema of the articular and periarticular structures with serous effusion into the joint space. Arthritis of rheumatic fever characteristically heals without residual manifestations because it does not cause erosion of the joint surface or lead to pannus formation.

Subcutaneous Nodules

These resemble Aschoff's nodules but heal rapidly without sequelae. They consist of a central zone of fibrinoid necrotic material surrounded by histiocytes, fibroblasts, and lymphocytes.

Chorea

Because patients with Sydenham's chorea rarely die during the active stage, pathological findings from chorea patients in the central nervous system have not been extensively studied. No characteristic lesion has been found that explains chorea. Perivascular changes in the brains of patients dying of fulminant rheumatic carditis occur whether or not chorea is present.[69]

Pleurisy and Pneumonitis

Pleurisy and pneumonitis may occur with exudative lesions. They only occur with severe carditis and can resemble the lung changes seen with pulmonary infarctions and heart failure. It is not known whether these are primary rheumatic manifestations or secondary to heart failure.

CLINICAL MANIFESTATION

It is important to make the diagnosis of rheumatic fever because subsequent serious cardiac disease can be prevented or minimized by long-term antistreptococcal prophylaxis. Clinical presentation and manifestations are extremely variable. The initial illness may appear acutely with fever and polyarthritis or may be subclinical until mitral stenosis is evident later in adult life. Unfortunately, there is no single clinical sign or laboratory test that is pathognomonic of rheumatic fever.

One typical feature is a latent period between streptococcal infections and RF varying from 7 to 35 days with an average of 18 days.[34] The latent period may be from 2 to 6 months in patients with Sydenham's chorea.[35]

The most commonly used criteria for diagnosis of rheumatic fever are the modified Jones criteria[71] enumerated in Table 86–1. According to these modified criteria, it is mandatory to demonstrate evidence of recent streptococcal infection (usually by elevation of antistreptolysin O titer) and to identify either one major plus two minor criteria or two major criteria. The minor manifestations are less specific for the illness but certainly can indicate the presence of active inflammation in a patient who was previously diagnosed as having rheumatic fever or rheumatic heart disease.

MAJOR CRITERIA

Arthritis

Rheumatic arthritis affects mainly large joints, particularly the knees, ankles, elbows, and wrists. The affected joint is hot, red, and tender. Rheumatic arthritis moves rapidly from one joint to another, resulting in the typical picture of a migratory polyarthritis. Each joint usually remains inflamed for no more than a week before inflammation starts to subside. It is important to withhold antiinflammatory agents until signs and symptoms are sufficient for the recognition of migratory polyarthritis if the diagnosis is uncertain.

Polyarthritis occurs in about 75% of patients during the acute stage of the disease. Joint involvement is more common in older patients. Joint involvement is accompanied by a lower incidence of carditis and chorea.[72,73]

Table 86–1. Modified Jones Criteria for Diagnosis of Rheumatic Fever

Requirement for Diagnosis	*Major Criteria*
a) Two major criteria or	Carditis
b) One major plus two	Arthritis
minor criteria	Chorea
	Erythema marginatum
	Subcutaneous nodules
c) Plus evidence of previous	*Minor Criteria*
streptococcal infection:	
* Recent scarlet fever or	Previous rheumatic fever
* Raised antistreptolysin O	Arthralgia
(ASO) titre or	Fever
* Positive throat culture	Acute phase reactants
	First-degree atrioventricular block

Rheumatic polyarthritis characteristically responds to salicylates. Joints are left without any sequelae except for the very rare (Jaccoud's type) of deformity of the metacarpophalangeal joints.[73,74] This is a result of periarticular fibrosis rather than synovitis.

Acute polyarthritis is almost always associated with a high or rising titer or streptococcal antibodies. Arthritis usually occurs within 30 days after the onset of streptococcal infection, when the antibody titer is at maximum.

Carditis

Carditis is the most serious major manifestation of rheumatic fever, since it may cause acute heart failure or culminate in chronic valvular heart disease.

The incidence of clinically evident carditis in the initial attack of rheumatic fever varies from 40 to 50%.[75] Carditis in its most severe form is rare in the current era but can lead to heart failure and death. Usually, carditis causes no symptoms and is diagnosed during examination of the heart of a patient who has arthritis or chorea. If other symptoms of rheumatic fever are absent or if carditis is mild, carditis might not even come to medical attention during the acute stage. This fact accounts for patients who have rheumatic heart disease without a history of rheumatic fever. One common presentation, particularly in children, is an insidious form with low-grade or no fever, with vague or absent arthritis or arthralgia, but with severe cardiac involvement. Carditis with *recurrent* rheumatic fever may present as congestive heart failure in a patient with rheumatic heart disease who was previously compensated.

Residual valvular disease depends on the severity of the initial episode of carditis and on the subsequent prevention of recurrent rheumatic fever. In one long-term study,[76] the incidence of residual valvular heart disease was almost 0% in patients without evidence of carditis in the first episode of rheumatic fever as long as recurrences were prevented.

Patients with carditis in the initial episode of rheumatic fever usually develop residual rheumatic heart disease. If recurrences can be prevented, the long-term outcome is better. Carditis is more apt to recur if rheumatic fever occurs in patients who have had carditis in the initial attack, thus increasing the risk of severe residual heart disease.[77] Rheumatic carditis may be found to have clinical features of involvement of the endocardium (including the valves), myocardium, or pericardium but frequently a combination of all three. The unequivocal signs of carditis in a patient with rheumatic fever are (1) an organic heart murmur that was not previously present, (2) pericardial friction rub or effusion, and/or (3) cardiac enlargement with or without heart failure.

Valvulitis

Mitral Valvulitis. The mitral valve is the most common site of inflammation in the course of rheumatic fever. It is affected almost three times more frequently than the aortic valve.[78] It can be diagnosed by:

1. The development of a loud apical systolic murmur that radiates to the axilla accompanied by a muffled first sound and a third sound caused by the development of mitral insufficiency. A systolic murmur over the apex without these characteristics may be an innocent murmur or caused by the fever and not mitral valvulitis.
2. The occurrence of a mid-diastolic murmur over the apex

resulting from narrowing of the mitral orifice by the thickened edematous cusps. The murmur begins after a third sound and is low pitched and localized to the apex.[79] This murmur implies definite mitral valvulitis. This was the murmur described by Carey-Coombs. The term "Carey-Coombs" murmur has come to mean the diastolic murmur associated with mitral regurgitation of any cause. The murmur may persist, indicating permanent damage, but it frequently disappears for a variable time to develop later—because of development of adhesions between the valve cusps—as the diastolic murmur of mitral stenosis.

Aortic Valvulitis. Aortic valvulitis may occur alone or with mitral valvulitis and can be diagnosed by:

1. The occurrence of an early diastolic murmur over the base. The murmur is a soft, high-pitched decrescendo murmur heard immediately after the second heart sound. The murmur may appear early in the course of the disease and is a definite sign of aortic valvulitis. A wide pulse pressure characteristic of aortic insufficiency can be noted early in the course of rheumatic fever.
2. As in mitral valvulitis, a systolic murmur over the base occurs either from the fever or from aortic valvulitis. It is not as predictive a sign as is the diastolic murmur. The murmurs of mitral and aortic valvulitis may disappear or may be followed by the establishment of chronic valve regurgitation, stenosis, or both, according to the pathological process occurring in the valve. Regurgitation of the mitral or aortic valves, being caused by damage to the valve, takes a short time to develop. Stenosis of these valves resulting from union of mobile cusps takes a longer time to develop.

Myocarditis

Myocarditis is usually accompanied by valvulitis and leads to:

1. Tachycardia (out of proportion to the fever) that persists during sleep.
2. Rapid cardiac enlargement, particularly involving the left ventricle and left atrium.
3. Heart failure. Congestive heart failure is a serious complication of rheumatic fever and indicates significant myocarditis. It occurs in 5 to 10% of first attacks, but it is more common as a manifestation of recurrence. Shortness of breath, tachycardia, and gallop are important early signs of left ventricular failure. Unexpected weight gain, engorgement of neck veins, and enlargement of the liver are early signs of right ventricular failure. A chest roentgenogram might be very helpful in the diagnosis of incipient heart failure, and echocardiography might reveal evidence of myocardial dysfunction.

One must occasionally differentiate between tachypnea resulting from salicylism from that resulting from heart failure. A "gallop rhythm" should not be diagnosed unless there are other signs of carditis. Children with rheumatic fever frequently have a prominent third sound as well as tachycardia.

Pericarditis

Pericarditis, which may be dry or with mild effusion, is encountered in only 5 to 10% of patients with carditis.[74,80] The degree of pericarditis does not correlate with the degree of myocarditis. A pericardial friction rub is pathognomonic. The rub may be heard widely over the precordium or localized to a single area. Murmurs of valvulitis are usually heard in the patient who develops pericarditis. The pericardial friction rub may be so loud that cardiac murmurs are obscured. S-T segment elevation in the electrocardiogram is unusual. Echocardiography can be useful in detecting even small pericardial effusions.

Chorea

Rheumatic or Sydenham's chorea (St. Vitus' dance) is more common in females. This usually occurs without carditis or polyarthritis. Chorea has decreased in frequency in comparison with arthritis and carditis.

The onset is usually gradual. Emotional instability is often a prominent feature. Many children who have chorea are labeled as having behavioral problems until the problem is recognized.

There are involuntary, uncoordinated, purposeless jerky movements. The patient, after protruding the tongue for inspection, may withdraw it rapidly, snapping the jaws. Speech is usually indistinct. The hand grip is often unsustained and is known as the "milkmaid's hand." Flexion at the wrists and dorsiflexion of the finger occur in the outstretched hands, giving the appearance of the "silver fork" deformity caused by hypotonia. Objects are often dropped from the hands. Excitement, fatigue, and effort increase the movements; sleep causes them to disappear. Handwriting is particularly affected. Serial evaluation of the patient's handwriting is an objective way of following improvement.

The latent period for chorea after streptococcal pharyngitis is from 1 to 6 months.[81] As a result, by the time chorea is manifest, streptococcal antibodies and acute phase reactants are normal.

Chorea is a self-limiting disease. It lasts an average of 3 months but may last for as long as 6 to 12 months. A 30-year followup of a group of patients with rheumatic chorea revealed that 27% of these patients developed rheumatic heart disease.[82]

Subcutaneous Nodules

Subcutaneous nodules, a rare major criterion of rheumatic fever, occur with severe carditis.[83] The nodules vary in size from 0.5 to 2 cm and are attached to the tendon sheaths. They occur on the extensor surfaces of bony prominences, scapulae, and mastoid processes. They consist of a collection of Aschoff bodies but are evanescent.

Subcutaneous nodules are not pathognomonic of rheumatic fever, since they occur in rheumatoid arthritis and systemic lupus erythematosus.

Erythema Marginatum

Erythema marginatum is also very rarely seen today. Initially, there is an area of erythema with advancing margins that clears in the center (Fig. 86–6). This lesion is painless and not pruritic. Erythema marginatum is transient and is found chiefly over the trunk and inner aspects of the arms and thighs. The rash blanches on pressure.

Like subcutaneous nodules, erythema marginatum is a major manifestation of rheumatic fever, but it is not pathognomonic, having also been reported in drug reactions and glomerulonephritis.[84]

MINOR CRITERIA

The minor manifestations occur regularly in rheumatic fever. Because they are common to many inflammatory diseases, they

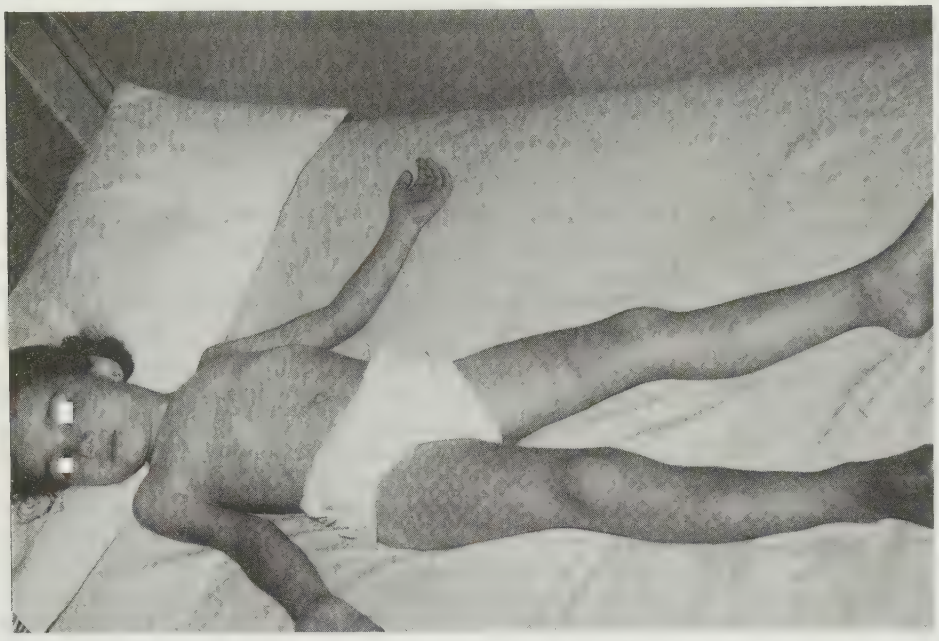

Fig. 86–6. A 6-year-old girl with erythema marginatum who had acute rheumatic fever with severe carditis. (Courtesy of Professor Samir Kassem, M.D., Alexandria Medical School.)

are of minor diagnostic value. They are helpful in diagnosing recurrent rheumatic activity in a patient who has already been diagnosed as having rheumatic heart disease. The minor criteria are listed in Table 86–1.

Fever

In the classical form, which is very rare nowadays, rheumatic fever starts with a fever between 100 and 104°F, which decreases in a few days to become low-grade or disappear. However, more often recorded is a low-grade fever from the start that might be found only in the afternoon. Rheumatic fever should not be diagnosed only on the basis of a prolonged fever unless there are other signs of the disease.

Arthralgia

Arthralgia in the form of dull, aching pains around the joints without objective findings is frequently noticed, particularly in patients with carditis. Arthralgia cannot be used as a minor criterion for diagnosis in patients with arthritis.

Abdominal Pains

Abdominal pains may occur early in the course of the disease even before arthritis. These pains may simulate acute appendicitis.[85] This pain is thought to be caused by vasculitis. Abdominal pain in rheumatic fever may also be epigastric from pericarditis, right hypochondrial from liver congestion, or caused by gastritis as a result of steroids or aspirin.

Pneumonia

Rheumatic pneumonia is rare and usually occurs with severe carditis. The pneumonia is characterized by marked tachypnea with little or absent rales. The chest roentgenogram shows a rapidly changing pattern that is suggestive of pulmonary edema migrating from one area of the lung to another.

Electrocardiogram

Long PR intervals are found commonly in acute RF but may be found in many other settings.

Laboratory Evidence Indicating Acute Infection

Laboratory evidence does not come from specific tests but is very important, since it indicates active disease. It includes elevated leukocyte count, high erythrocyte sedimentation rate, and presence of C-reactive protein.

Erythrocyte Sedimentation Rate

With the exception of established chorea, erythrocyte sedimentation rate is almost always elevated above 60 in the early part of the disease. Congestive heart failure may lower ESR, but not to normal levels. The ESR remains elevated for 6 to 12 weeks in untreated patients. Anti-inflammatory agents suppress the ESR coincident with suppression of the clinical signs of inflammation. Sometimes the ESR may remain moderately elevated without any other evidence of inflammatory activity.[86]

C-Reactive Protein

Like the ESR, C-reactive protein (CRP) rises in the acute phase of rheumatic fever and is not a specific test.

Complete Blood Count

A complete blood count usually demonstrates a moderate anemia, partly caused by increased plasma volume and decreased erythropoiesis.[79] Leukocyte count is increased to a moderate degree.

Serum Proteins

Like ESR, serum gamma globulins are usually elevated but are not a specific indication of rheumatic fever. Immunoglobulin A is also elevated, while immunoglobulin M is infrequently so.[87] A significant elevation of alpha macroglobulins (e.g., ceruloplasmin)

can be found in the early phase of rheumatic fever and falls toward normal, paralleling ESR.[88]

Evidence of Previous Streptococcal Infection

Streptococcal Antibodies

Specific antibody tests are generally reliable methods of obtaining evidence of recent streptococcal infection. Titers obtained with these specific antibody tests may be elevated even in the absence of clinical or current bacteriologic evidence of streptococcal disease. Antibody responses may be suppressed by antibiotic therapy and may be suppressed or delayed by steroid therapy.

Antibodies used to diagnose antecedent streptococcal infection have included antistreptolysin O (ASO), antideoxyribonuclease-B, antistreptodornase, antidiphosphopyridine nucleotidase (anti-DPNase), antistreptokinase, antihyaluronidase, and antistreptococcal esterase.

The antistreptolysin O antibody is abnormally elevated in 70 to 85% of patients with acute RF. A single value of 500 units is considered indicative of recent streptococcal infection, and a value of 333 units is of borderline significance. If antistreptolysin O titer is 333 or less, additional antistreptococcal antibody assays should be obtained. These include antideoxyribonuclease-B (antistreptodornase),[88] antidiphosphopyridine nucleotidase (anti-DPNase),[89] antihyalurinidase, antistreptococcal esterase,[69] and antistreptokinase.[90] When three different streptococcal antibodies are measured, more than 95% of patients with acute RF have abnormal elevation of at least one of them. The streptozyme test[91,92] includes an assay for antibodies against five extracellular antigens of Group A streptococci (streptolysin O, hyaluronidase, streptokinase, deoxyribonuclease B, and nicotinamide adenine dinucleotidase). Unfortunately, false positive streptozyme tests are common,[93] and we do not recommend the use of the streptozyme test alone as a screening test. The streptozyme test is useful in conjunction with a negative or borderline antistreptolysin O titer. A negative streptozyme test with a negative or borderline antistreptolysin O titer indicates that recent streptococcal infection is unlikely.

These antistreptococcal antibody tests are specific only for streptococcal infection and not for acute rheumatic fever. The major contribution of these tests is to provide assurance that the disease entity under consideration has been preceded by an illness that could have resulted in rheumatic fever. Some authors[94] have recommended testing three antibodies (e.g., ASO, ASKase, and ADNase-B) at a time. If two of the three titers are positive, one can make the diagnosis of fairly recent streptococcal infection. If only one of the three titers is positive, previous or nonspecific causes of the antibody rise should be considered.

The determination of antibodies to the group A carbohydrate (A-CHO) moiety of the streptococcal cell wall has not been selectively helpful in the diagnosis of acute rheumatic fever. However, because antibodies to group A carbohydrate remain for several years in patients with persistent rheumatic valvular disease, this test could aid in the differentiation of rheumatic from nonrheumatic heart disease.[87,95]

Throat Culture

A throat culture is of little practical value. Since there is usually a latent period of 1 to 3 weeks between pharyngitis and the appearance of rheumatic fever, a throat culture taken at the onset of rheumatic fever is frequently negative. A throat culture that shows streptococci does not prove recent infection, since children can be streptococcal carriers.

History of Scarlet Fever

When present, scarlet fever is usually a reliable indicator of preceding streptococcal infection.

THE CHANGING PICTURE OF RHEUMATIC FEVER

Over the years, there have been changes not only in the occurrence of rheumatic fever but also in its severity, presentation, clinical manifestations, and possibly cause.

Several reports have described the virtual disappearance of rheumatic fever in different areas of the United States.[96,97] However, there are differences among reports[98,99] as to whether these trends apply to all racial, socioeconomic, and geographic subgroups. Most studies have indicated a higher incidence of rheumatic fever in blacks, native Americans, and the poor. A review[100] of mortality and morbidity statistics of the U.S. National Center for Health Statistics showed that similar changes have occurred nationwide for acute rheumatic fever but not for chronic rheumatic heart disease, which still causes considerable mortality, morbidity, and utilization of costly surgical facilities. The age-adjusted mortality rate per 100,000 for the combined category of rheumatic fever and rheumatic heart disease has declined in the United States from 14 in 1950 to 2.2 in 1982. In 1982, however, an outbreak of rheumatic fever was noted in the intermountain area of the western United States with an eightfold increase over the average annual incidence from the same area.[6] In developing countries, rheumatic fever and rheumatic heart disease remain a major public health problem.[101,102] A recent large survey in India found that between 200 and 1200 children per 100,000 are afflicted with rheumatic fever annually.

Not only is the occurrence of rheumatic fever less in developed countries, but when it occurs, it tends to be mild. In many tropical and subtropical less developed countries, chronic rheumatic heart sequelae are not only common but assume a malignant form (Figs. 86–7 to 86–10). Many of these patients have severe pulmonary hypertension[103] and require surgery at a young age.

In areas where rheumatic fever is still common, it has been noted that the disease runs a subacute rather than an acute course. Joint involvement is less conspicuous. Rheumatic nodules and erythema marginatum are becoming very rare, but chorea is still seen. Chronic active forms are common; the acuteness of the symptoms has subsided, but the severity of cardiac process has not ameliorated. This is in contrast to the European and U.S. experience, in which both the acuteness and severity of rheumatic fever have decreased.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diagnosis of rheumatic fever is not an easy task today, except in florid, clear-cut cases. The Jones criteria and the revised modification two decades later leave much to be desired.[104,105] The criteria are not sensitive enough to include mild cases and not sufficiently specific, since other conditions may be wrongly diagnosed as rheumatic fever. As a result, both overdiagnosis and

Fig. 86–7. A young, underdeveloped Egyptian female, 11 years old, with recurrent rheumatic fever on top of mitral and aortic rheumatic valve disease. This is a common problem in many developing nations where rheumatic fever and multivalvular heart disease with gross cardiomegaly is seen at such a young age.

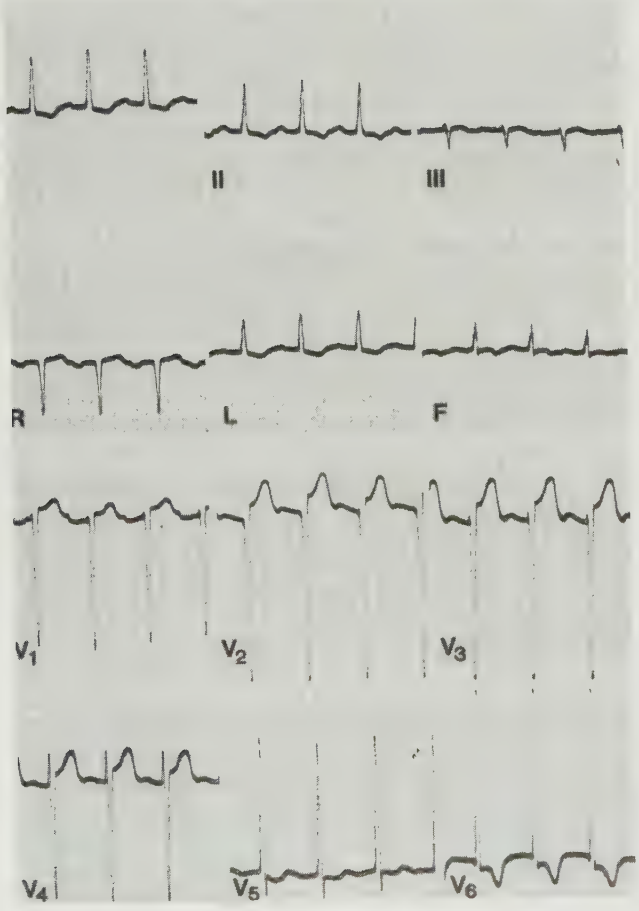

Fig. 86–8. The electrocardiogram of the patient of Fig. 86–7 showing sinus tachycardia, a prolonged P-R interval, left ventricular hypertrophy, and strain.

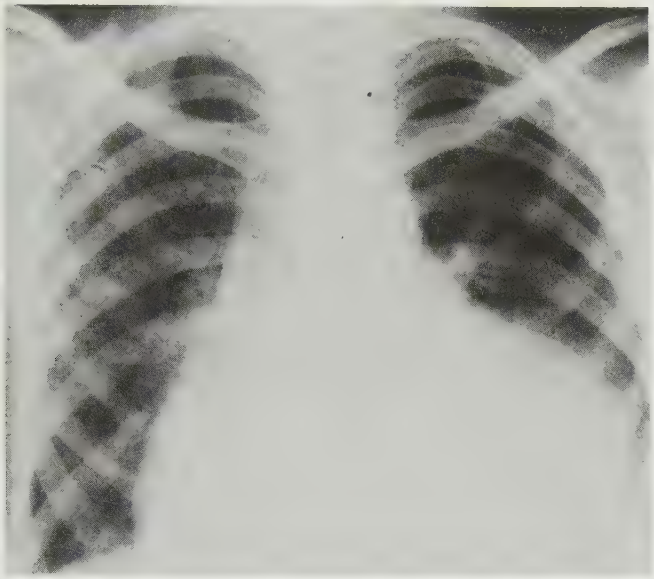

Fig. 86–9. Posteroanterior chest roentgenogram of the patient of Fig. 86–7 depicting gross cardiomegaly.

underdiagnosis occur. This fact should be taken into consideration in examining a patient who is suspected of having rheumatic fever.

Fever and Arthritis

Fever and arthritis must be differentiated from other causes of polyarthritis in children.

Juvenile Rheumatoid Arthritis

Rheumatoid arthritis in its early phase, when it involves big joints, may be difficult to differentiate from rheumatic polyarthritis. The points in favor of rheumatoid arthritis rather than rheumatic fever include involvement of small joints, particularly the hands and feet; morning stiffness; fusiform swelling of fingers and joint deformities; lymphadenopathy; splenomegaly; and absence of antistreptococcal antibodies.

Infective Endocarditis

Unexplained fever and arthralgia in a patient with rheumatic heart disease may be rheumatic reactivation or infective endocarditis. The points in favor of infective endocarditis would include petechiae, hematuria, clubbing, splenic enlargement, embolic findings, and positive blood culture.

Sickle Cell Anemia

In sickle cell anemia, which is caused by microvascular thrombosis, there may be manifestations like those of rheumatic fever such as joint pains, fever, heart murmurs, cardiac enlargement, and abdominal pain. Hemoglobin electrophoresis is diagnostic.

Polyarthritis

Polyarthritis occasionally is seen with bacterial infections such as pneumococcal, gonococcal, meningococcal, and staphylococcal infections. These can usually be diagnosed by blood or joint cultures. Osteomyelitis might simulate rheumatic fever if pain is referred to a big joint.

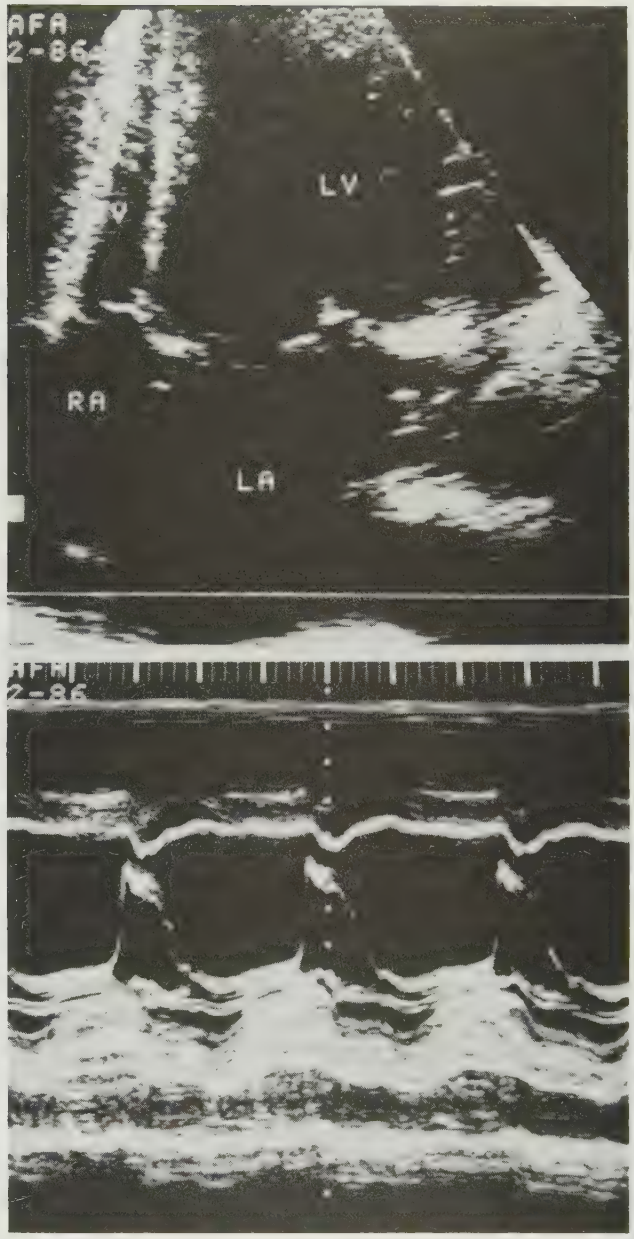

Fig. 86–10. Two-dimensional and M-mode echocardiograms of the patient of Fig. 86–7. (top) Apical four-chamber view showing a dilated left ventricle and left atrium and thickened mitral valve. (bottom) M-mode echocardiogram at the level of the mitral valve showing thickened mitral valve and pericardial effusion.

Immune Complex Disease

Immune complex disease may also resemble rheumatic fever. A notable example is serum sickness.

Carditis

The heart murmurs of rheumatic fever must be differentiated from functional murmurs, mitral valve prolapse, myocarditis, pericarditis and congenital heart disease.

Functional Murmurs

Functional murmurs may create confusion. Fever increases the intensity of the functional murmur.

Myocarditis

Viral and other forms of myocarditis may be difficult to differentiate from rheumatic fever, especially if the extracardiac manifestations of rheumatic fever are absent. Myocardial biopsy might be helpful.

Pericarditis

Primary viral pericarditis may be confused with an early case of rheumatic fever,[106] but the appearance of other manifestations of rheumatic fever and antistreptococcal antibodies are of great help in differentiation.

Mitral Valve Prolapse

Mitral valve prolapse and congenital anomalies affecting the mitral valve may at times create problems. The murmur of mitral prolapse increases with fever and can be confused with mitral valvulitis. The absence of other manifestations of rheumatic fever and high antistreptococcal titers help in differentiation. The echocardiogram is also characteristic. It has been suspected, however, that rheumatic mitral involvement may be a cause of mitral valve prolapse.

COURSE AND PROGNOSIS

The clinical course of patients with rheumatic fever is extremely variable, but there is usually a characteristic sequence and predictable duration for the major manifestations.

The onset of disease is usually abrupt in patients whose initial manifestations are fever and arthritis. The disease begins much more insidiously in patients presenting with Sydenham's chorea. Carditis also may be subtle in its appearance and may be unsuspected until a murmur is heard on physical examination.

The presence or absence of carditis is an important determinant of the course and prognosis of acute rheumatic fever. The incidence of carditis depends on age. In one study, before the age of 3 years, 90% of patients had carditis.[101] The incidence of carditis decreased to 50% in the 3- to 6-year-old age group, and to 32% in the 14- to 17-year-old age group.[107] After the age of 25, carditis was very rare with the first attack of rheumatic fever. The duration of rheumatic activity is longer in patients with carditis than those without cardiac involvement.[108] The usual duration is rarely longer than 3 months even when severe carditis is present. In fewer than 5% of patients, rheumatic fever may remain active for more than 6 months.[86] These patients are considered to have a state of chronic active carditis.

The prognosis is excellent for subjects who escape carditis during an initial attack of rheumatic fever.[74,109] The prognosis worsens with increasing severity of initial carditis and with recurrences.

The mean duration of rheumatic activity is shortest when no suppressive drugs are given.[108] Rheumatic activity appears to be prolonged when rebounds of activity occur after withdrawal of antirheumatic drugs. Suppressive therapy masks the inflammation but does not terminate the process and may actually prolong it.

RECURRENCE OF RHEUMATIC FEVER

First attacks of rheumatic fever in the general population following epidemic streptococcal pharyngitis average 3%. Such infections in patients with a history of previous but recent rheumatic fever may produce a secondary attack rate as high as 65%.[11] The rheumatic attack rate decreases with the passage of time[103] to reach about 4 to 8% ten or more years after the last attack. Another factor that increases the chance that a second streptococcal infection will be followed by a rheumatic attack is the presence of residual valvular heart disease.[50]

Any patients with rheumatic valvular disease and a fever of unknown cause should be suspected of recurrent rheumatic activity, especially if there is evidence of streptococcal infection.

TREATMENT

Prophylactic

The most effective preventive measures against rheumatic fever are socioeconomic and sanitary. Adequate housing and relief of crowding are important in prevention of streptococcal infections.

Primary Prophylaxis

The aim of primary prophylaxis is to prevent the initial attacks of rheumatic fever by identification and treatment of the streptococcal pharyngitis. Effective prevention demands the eradication of the infecting organism. A single intramuscular injection of benzathine penicillin (600,000 units in children under 25 kg and 1.2 million units in those over 25 kg) is the most effective method.[110] This is preferred to oral penicillin, which requires 10 successive days of treatment. For patients who are allergic to penicillin, erythromycin (25 mg/kg/day) is given for 10 days. Primary prophylaxis proved to be very effective in military populations with a high frequency of streptococcal infections, with a reduction of the attack rate of rheumatic fever from 3% to 0.3%.[111]

Mass antibiotic prophylaxis by intramuscular administration of 1.2 million units of benzathine penicillin to all members of an affected population has been effective.[112–114] This approach can be applied if possible in civilian epidemics. On the other hand, with the marked decline in streptococcal pharyngitis and rheumatic fever in many populations, the need for treatment of simple pharyngitis with penicillin has been questioned. In these populations, selective throat cultures for beta-hemolytic streptococci should be made. A negative culture makes antibiotic therapy of simple sore throat unnecessary more than 95% of the time.[115]

At present, there is no effective vaccine against streptococcal infections for general use, although one is under investigation.[116] The clinical and epidemiologic efficacy of a streptococcal vaccine has not been conclusively demonstrated. Recent studies have suggested that it might be possible to induce antibodies with small doses of purified M-protein.[117] Recent advances in the purification of M-proteins and definition of their molecular structure have provided encouraging data that could ultimately make the approach to a group A streptococcal vaccine more feasible.[19,118]

Secondary Prophylaxis

Secondary prophylaxis is the prevention of recurrences of rheumatic fever by continuous chemoprophylaxis. The most effective has been a single monthly intramuscular injection of 1.2 million units of benzathine penicillin.[119] Oral penicillin prophylaxis consists of 500 to 1000 mg of penicillin twice daily. If the patient is allergic to penicillin, chemoprophylaxis can be achieved with 250

mg of erythromycin twice daily. Oral sulfonamide prophylaxis is no longer used because of side-effects and the appearance of resistant streptococcal strains.

The injectable form of prophylaxis is more effective than the oral form. In the Irvington house study, the attack rate with the injectable form of prophylaxis was one recurrence per 250 patient years compared with ten recurrences per 250 patient years with oral prophylaxis.[111] Allergic reactions with the injectable forms are more serious than with the oral penicillin, but such reactions are extremely rare after the first months of prophylaxis. There is considerable controversy about duration of prophylaxis. The American Heart Association recommends prophylaxis for life. In Egypt, we administer prophylaxis until the patient is 25 years old or for 10 years after the last rheumatic fever attack.

Tonsillectomy was at one time almost a routine procedure in rheumatic subjects. Although there is some evidence that tonsillectomy may reduce the frequency of clinically apparent streptococcal infection and large tonsils are associated with increased frequency of recurrences in rheumatics with poor prophylactic compliance, there is no evidence that tonsillectomy reduces the attack rate of rheumatic fever.[120]

Treatment of Acute Rheumatic Fever

Rest

Patients with rheumatic fever must remain in bed during the acute and febrile portion of the illness. Light physical activity can be allowed once the acute febrile illness has abated and signs of carditis have stabilized. Children with polyarthritis alone can usually go to school in 4 to 6 weeks following the onset of symptoms. Patients with carditis should have rest until signs of cardiac inflammation subside. Strenuous activity and physical exercise are not allowed in any patient before 2 to 3 months.

Diet

No special diet is necessary unless heart failure is evident, in which case salt should be restricted.

Penicillin

Once the diagnosis has been made, a course of penicillin adequate to eradicate residual group A streptococci must be given even if a throat culture is negative. A single injection of 1.2 million units of long-acting penicillin is adequate. Secondary prophylaxis must start immediately.

Anti-inflammatory Agents

The administration of these agents should be delayed until a proper clinical and laboratory diagnosis has been established. Premature administration of these agents to a patient with arthralgia or early monoarticular arthritis might mask the disease process and cause diagnostic confusion.[108]

The antirheumatic agents used, whether salicylates or corticosteroids, are valuable symptomatic and supportive drugs. However, they are not curative and might actually prolong the course of the disease. The outcome of rheumatic fever has not been affected by the antirheumatic agent selected.[74,109,121]

Aspirin. Acetyl salicytic acid (aspirin) is analgesic and antipyretic and generally makes the patient feel better. It causes dramatic improvement of the arthritis to the extent that it can be given as a therapeutic test, but it is without effect on carditis.

Indications: Aspirin is given to patients without carditis if there are side-effects or contraindications to the use of corticosteroids and during and after withdrawal of corticosteroids.

Toxicity: Side-effects of aspirin include tinnitus, gastric irritation, bleeding tendency, metabolic acidosis, hyperventilation and respiratory alkalosis, idiosyncrasy, and hypoglycemia.

Dosage: The usual dose is 90 to 120 mg/kg (one grain per pound) body weight/day divided into every four-hour interval doses until a satisfactory clinical response is obtained. A serum salicylate level between 15 and 25 mg/100 mL gives optimal therapeutic effect. The dose is then reduced to two thirds and continued until inflammation subsides clinically (or, according to some practitioners, until all laboratory manifestations are normalized). This usually takes 6 to 9 weeks. After this, the dose is gradually decreased to avoid the rebound that occurs if the drug is stopped abruptly.

Corticosteroids. Neither salicylates nor corticosteroids guarantee termination of the disease and its cardiac damage. However, steroids result in more prompt resolution of the inflammatory process than aspirin and so can decrease the load on the heart.[107,121,122]

Indications: Corticosteroids are indicated for patients with moderate carditis if the disease is not adequately suppressed by salicylates or if salicylates are not tolerated.

Dosage: The usual dose is 2 mg/kg/day of prednisone or prednisolone, not to exceed 60 mg/day for 3 to 4 weeks.

Many controlled studies have been done comparing aspirin with corticosteroids. Some support the use of steroids,[122,123] and others did not find any benefit.[109,124] At present, no firm conclusions about the place of steroids in preventing the development of rheumatic heart disease can be reached. In most cases, carditis appears early in the course of rheumatic fever,[102] and regardless of treatment, the risk of developing subsequent heart disease is probably minimal in patients who do not have carditis at the time of admission to the hospital or at the time treatment is begun.[122] It seems reasonable to limit consideration of the use of steroids to patients who exhibit carditis of at least moderate degree, especially those with evidence of heart failure. Patients who have arthritic disease alone or who have only mild or questionable carditis can usually be treated well with aspirin.

Treatment of Chorea

Patients must be cared for in a quiet environment protected against self-inflicted injury caused by uncontrollable movements. Chlorpromazine or diazepam[125] can be used as sedatives. Barbiturates may cause agitation. Haloperidol (butyrophenone) is the most effective drug in controlling the abnormal movements, but extrapyramidal reactions have been reported.[126] Patients with concomitant rheumatic activity can be given aspirin, and those with carditis may receive steroids. There is no definitively known value of steroids or aspirin on the course of chorea itself.

Treatment of Heart Failure

Heart failure, if present, is treated in the usual ways with diuretic therapy and digitalis.

Surgical Treatment

Surgical treatment is resorted to rarely as a life-saving measure if there is gross mitral and/or aortic valve insufficiency and the patient is not improving on vigorous medical treatment.

Plasmapheresis

Since rheumatic fever patients have circulating immune complexes in their blood that might be the cause of the cardiac damage, plasmapheresis has been reported in three cases of rheumatic fever with improvement of abnormal clinical and laboratory findings as well as marked reduction of the high levels of circulating immune complexes.[126]

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CHAPTER 87

Rheumatic Heart Disease

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Chronic rheumatic heart disease, like rheumatic fever, is most common in areas where the standard of living is low. The decline in the frequency and severity of rheumatic heart disease in Western Europe and the United States, which started even before antibiotics became available, is attributed mainly to improved socioeconomic standards.[1] Rheumatic heart disease is still one of the most important causes of heart disease in less developed areas. It constitutes 25 to 40% of government general hospital cardiac admissions in India, Egypt, Thailand, the Philippines, Jamaica, and Puerto Rico. In these areas, rheumatic fever and its recurrences are not only common but also assume a malignant form, leading to well-established and significant valvular heart disease in children, often with pulmonary hypertension.[2] Many of these patients either need surgery or succumb before the age of 20. In children and adolescents, the mitral valve is involved in 85% of cases, the aortic valve in 54%, and the tricuspid and pulmonary valves in less than 5%.[3]

RHEUMATIC MITRAL INSUFFICIENCY

Healing of acute rheumatic mitral valvulitis may cause mitral insufficiency and/or stenosis, depending in part on the resultant physical orientation of the mitral leaflets. Mitral regurgitation is the most common chronic rheumatic heart disease in children and adolescents. Mitral stenosis is usually associated with mitral regurgitation. Mitral insufficiency results from fibrosis and contracture of the valve leaflets so that they cannot efficiently coapt.[3] The severity of the lesion is variable. In patients with severe mitral regurgitation, there is disorganization of the valve mechanism and shortening of the valve cusps, chordae tendineae, and papillary muscles (Fig. 87–1). In advanced and long-standing cases, the inflamed leaflets calcify. Calcification may extend from one leaflet to the other across one or both commissures, keeping the two leaflets apart at the involved commissure. As the left atrium enlarges from the insufficiency, it displaces the posterior leaflet posteriorly, while it is restrained at the opposite end by its tensor apparatus. The result is that the posterior leaflet may lose its capability to move. The increase in mitral insufficiency initiates a vicious circle wherein "mitral insufficiency begets mitral insufficiency."[4]

Pathophysiology

As the left ventricle contracts, part of its stroke volume regurgitates to the left atrium through the incompetent mitral valve. Because of the pressure difference between the left ventricle and the left atrium, regurgitation starts during the phase of isometric contraction of the left ventricle, and almost half of the regurgitant volume is ejected into the left atrium before the aortic valve opens.[5] The volume of regurgitation depends on the size of the regurgitant orifice as well as on the pressure gradient between the left ventricle and the left atrium.[6] The amount of left ventricular stroke volume ejected into the left atrium influences the degree of left atrial enlargement as well as left ventricular dilatation.[7] The systolic regurgitant flow produces the characteristic prominent v wave in the left atrium. The increased diastolic transmitral volume flow produced by the blood that leaked during the previous systole in addition to the pulmonary venous return produces a flow murmur that can mimic mitral stenosis (Carey Coombs murmur, in conventional usage).

Fig. 87–1. Opened specimen showing severe rheumatic mitral insufficiency. The leaflets, chordae tendineae, and papillary muscles are fibrosed and retracted. The left ventricle is dilated. (Courtesy of Dr. Soheir Mahfouz, Pathology Dept., Cairo University.)

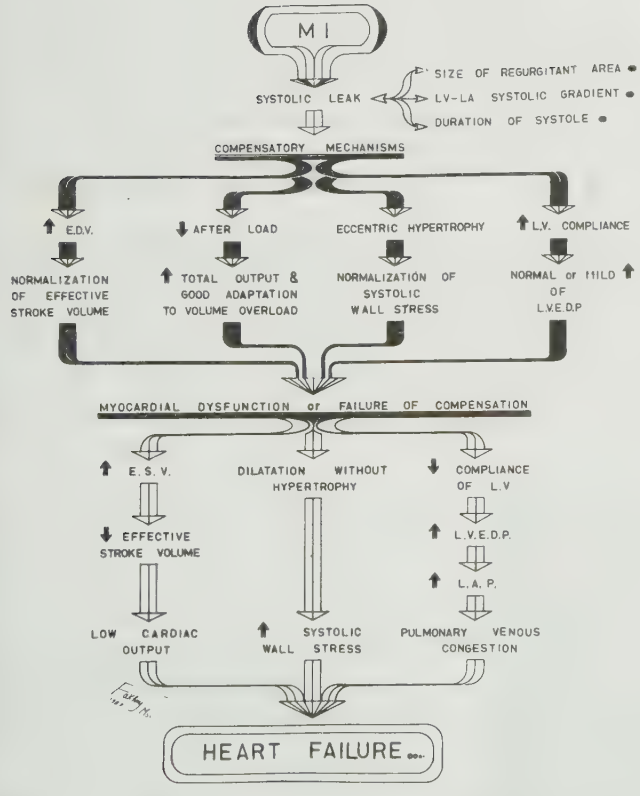

Fig. 87–2. A diagram depicting factors that determine the degree of regurgitation, compensation, and decompensation in mitral insufficiency.

Compensation in chronic mitral insufficiency (Fig. 87–2) includes dilatation of the left ventricle to accommodate the increased filling volume. The increase in left ventricular end-diastolic volume permits a large stroke output. This maintains forward systemic flow. The increase in left ventricular end-diastolic fiber length is not initially reflected in an increase in end-diastolic pressure because of the increase of left ventricular distensibility (compliance). An increase in left ventricular as well as left atrial compliance in chronic mitral insufficiency reduces the extent of pulmonary congestion. After dilatation, hypertrophy occurs to normalize wall stress.[8]

The resistance to ventricular emptying (left ventricular afterload) is reduced because of the systolic regurgitation. This systolic unloading of the ventricle is a reason why patients with chronic mitral insufficiency remain well for many years.[9] The reduced load on the left ventricle allows a greater proportion of the contractile energy of the myocardium to be expended in shortening rather than in tension development. As a consequence of reduced afterload, patients with severe mitral insufficiency may show a small increase of ejection phase indices of myocardial contractility, such as ejection fraction and velocity of circumferential fiber shortening.[10]

As mitral insufficiency persists, the above-mentioned compensatory mechanisms (namely, increased preload, increased compliance, increased wall thickness, and decreased afterload) will not be sufficient because of the impaired myocardial contractility that is characteristic of chronic overload. Symptoms of low cardiac output and of lung congestion develop. Changes of impaired myocardial contractility may be found before symptoms appear by end-diastolic stress volume indices,[11] which are relatively independent of loading conditions.

Symptoms

Since symptoms in chronic mitral insufficiency do not develop until the left ventricle fails, the time interval between the attack of rheumatic fever and the development of symptoms tends to be longer than in mitral stenosis, often exceeding two decades. Also, in contrast to mitral stenosis, symptoms of low cardiac output are more prominent and appear before symptoms of lung congestion. The gradual onset of dyspnea can progress to paroxysmal nocturnal dyspnea. However, the incidence of acute pulmonary edema is lower than in mitral stenosis because sudden elevations in left atrial pressure are less frequent.[12] Similarly, while hemoptysis and systemic embolization do occur in mitral insufficiency, they are less common than in mitral stenosis. The development of atrial fibrillation affects the course of the disease adversely, but not as dramatically as in mitral stenosis because left atrial pressure is not as severely elevated by atrial fibrillation in mitral regurgitation as in mitral stenosis.[12] Atrial fibrillation is also more common in mitral stenosis.

General Examination

The heart rate and blood pressure are usually normal. The peripheral arterial pulse is small in volume but often exhibits a brisk upstroke. Atrial fibrillation may develop in the later stages of the disease.

Precordial Examination

The cardiac impulse is diffuse, forceful, and displaced downward and laterally. A prominent left ventricular filling wave is

frequently palpable in early diastole. An aneurysmally dilated left atrium may produce visible and palpable pulsations to the right of the sternum.

Auscultation

The first heart sound is usually diminished unless the pathological process involves predominantly the posterior leaflet and spares the anterior leaflet.

Wide splitting of the second heart sound is common because of an earlier aortic component of the second sound. This splitting is possibly related to shortened left ventricular ejection time resulting from the diminished afterload.

A loud apical third sound is usually audible because of increased transmitral volume flow during the rapid filling phase.

The characteristic murmur of mitral insufficiency is a high-pitched holosystolic murmur beginning with the soft first sound and continuing beyond (and sometimes obscuring) the second sound. The murmur is loudest at the apex with radiation to the axilla and left infrascapular area. Radiation toward the sternum or aortic area may occur with posterior mitral leaflet regurgitation. There is little correlation between the intensity of the murmur and severity of the lesion. Mitral insufficiency murmurs diminish with maneuvers that decrease afterload, such as standing and amyl nitrite inhalation, and increase with maneuvers that increase afterload, such as squatting and phenylephrine infusion.

Electrocardiography

In chronic mitral insufficiency, the electrocardiogram exhibits evidence of left ventricular and left atrial enlargement. In an advanced case, atrial fibrillation may supervene. Approximately 15% of patients with chronic mitral insufficiency exhibit electrocardiographic evidence of right ventricular hypertrophy, and 5% show combined ventricular hypertrophy.[13]

Radiography

Early in the course of the disease, the cardiac shadow may be normal. Later, left atrial and left ventricular enlargements become evident. The left atrium is generally more enlarged in mitral incompetence than in mitral stenosis (Fig. 87–3). Pulmonary hilar congestion with redistribution of flow to upper lobes, interstitial edema, and Kerley B lines appear with the development of left ventricular failure. Fluoroscopy may show systolic expansion of the left atrium. Calcification of the mitral valve is less common than in mitral stenosis and, when present, usually represents a mixed lesion.

Echocardiography

Echocardiography is useful not only in identifying the etiology of mitral insufficiency but also in determining its degree, in evaluating left ventricular function, and in determining the prognosis after mitral valve replacement.

M-Mode Echocardiography

Since mitral stenosis and insufficiency often coexist in rheumatic heart disease, an M-mode echocardiogram of the mitral valve often shows also the typical signs of mitral stenosis.[14] A number of M-mode echocardiographic signs, such as excessive mitral valve motion and a steep E-F slope,[15] suggest chronic mitral regurgitation. However, these signs do not constitute a specific finding for mitral insufficiency, since they can be observed in a variety of conditions that cause an increase in mitral valve flow. Furthermore, if there is fibrosis from rheumatic mitral disease, mitral valve motion is diminished.

Exaggerated septal motion is common in patients with chronic mitral insufficiency, but this sign may also be found in patients with other causes of volume overload of the left ventricle, particularly aortic regurgitation.

Increase in left ventricular diastolic dimension and significant decrease in left ventricular diameter during the pre-ejection phase can be detected. The latter sign is caused by the loss of the isovolumic contraction period because of the incompetent valve.[16]

A dilated left atrium and systolic expansion of the posterior left atrial wall have been proposed as useful signs of mitral insufficiency[17] (Fig. 87–4). However, these posterior left atrial wall pulsations are infrequently seen with mitral regurgitation. Furthermore, a similar finding has been noted in normal subjects and in patients with ventricular septal defect.[18] No clear correlation was found between the severity of the disease and left atrial diameter.[19]

Although none of these M-mode echocardiographic findings is specific for the diagnosis of chronic mitral insufficiency, a combination of these findings in conjunction with the appropriate clinical picture is helpful. M-mode echocardiography may also be of value in terms of prognosis in patients with mitral insufficiency. Persistence of symptoms and poor long-term prognosis have been observed after mitral valve replacement if the left ventricular end-

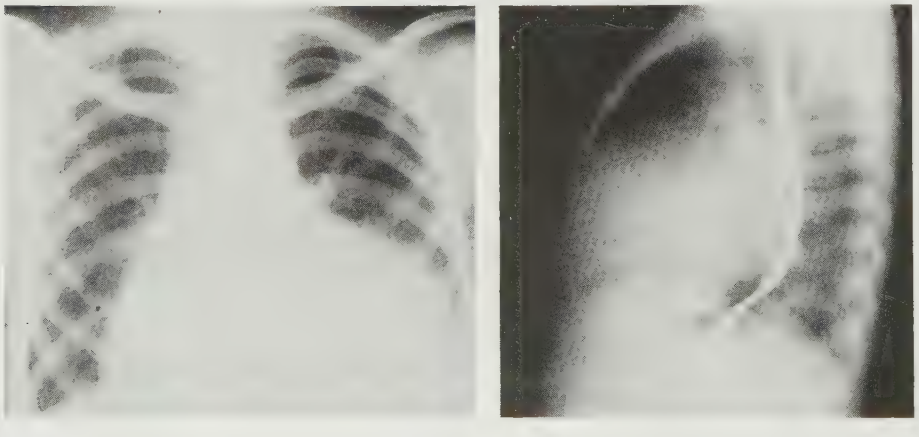

Fig. 87–3. Posteroanterior and lateral chest radiographs from a patient with advanced rheumatic mitral and aortic valve diseases showing gross cardiac enlargement.

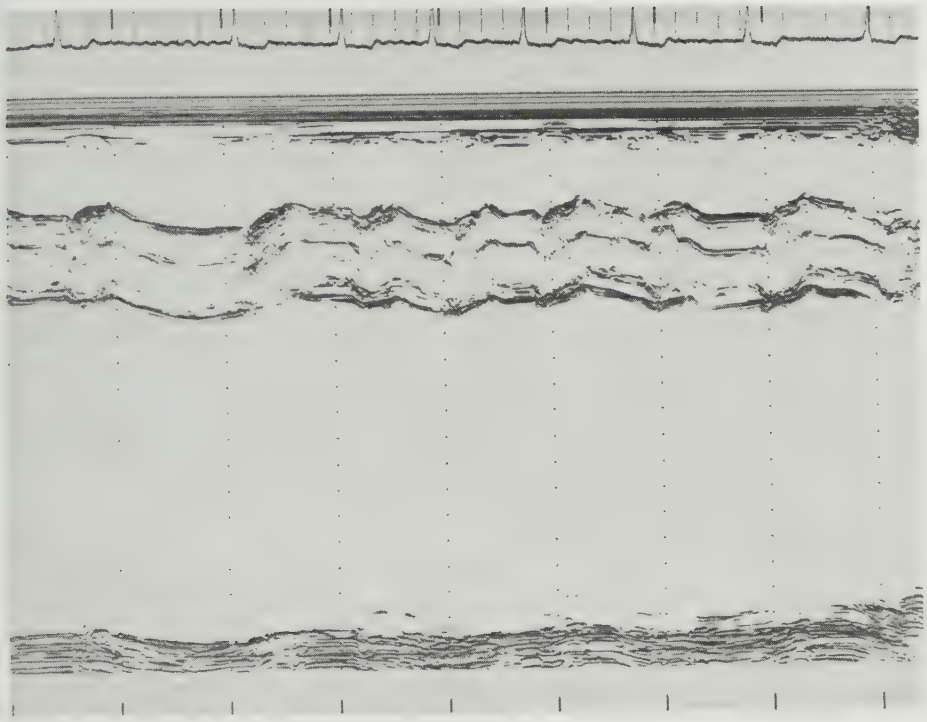

Fig. 87–4. M-mode echocardiogram showing aneurysmal left atrium (12 cm) from a patient with severe mitral insufficiency and mitral stenosis.

systolic dimension exceeds 2.6 cm/m², the end-diastolic dimension exceeds 4 cm/m², or the fractional shortening was less than 31%.[20,21] Symptomatic improvement after mitral valve replacement has been associated with a decrease in left atrial size postoperatively.[19] Persistent left atrial dilatation with atrial fibrillation after mitral valve replacement for mitral regurgitation has also been found to indicate a poor prognosis.

Two-Dimensional Echocardiography

Two-dimensional echocardiographic findings in rheumatic mitral regurgitation include thickened mitral valve leaflets, incomplete closure of the mitral valve, relatively immobile posterior mitral leaflet, dilated left atrium with systolic expansion, and dilated left ventricle with hyperdynamic septal and posterior wall motion.[14]

Doppler Echocardiography

Doppler echocardiography has an important role in both diagnosis and quantification of mitral insufficiency with a very high degree of specificity and sensitivity.[19,23,24]

The degree of mitral insufficiency can be assessed by the depth of extension of the regurgitation into the left atrium, by the intensity of the Doppler signal from the regurgitation, and by increases in forward flow velocity.[19,23–25]

Using color Doppler flow mapping, only a weak relationship has been observed between jet size and regurgitant volume or fraction. No correlation is found between jet size and any measurement of cardiac pressure or flow. However, a general correlation was observed between jet size and end-diastolic volume index, a finding suggesting that color Doppler flow mapping may reflect the volume overload imposed by mitral regurgitation.[26]

Radioisotope Angiography

Radionuclide techniques can measure the end-diastolic and end-systolic volumes, estimate the regurgitant fraction, and assess the left ventricular function by estimating the ejection fraction.[27,28]

Cardiac Catheterization and Angiography

Cardiac catheterization usually demonstrates elevated left atrial pressure. The v wave is particularly elevated. There is a prompt Y descent unless mitral stenosis is associated. The effective forward cardiac output is usually depressed. The total left ventricular output (forward and regurgitant) is usually elevated unless left ventricular dysfunction supervenes. Although a left atrioventricular pressure gradient persisting throughout diastole signifies the presence of associated mitral stenosis, an early diastolic gradient may occur in patients with severe regurgitation as a result of torrential blood flow across a normal-sized mitral orifice. The pulmonary artery and right ventricular pressures may be elevated in severe long-standing cases associated with increased pulmonary vascular resistance.

The diagnosis of mitral regurgitation is usually established by means of left ventriculography. Mitral regurgitation is indicated by the appearance of contrast material in the left atrium following left ventricular injection. Mitral regurgitation due to rheumatic involvement is characterized by a central regurgitant jet and by thickened leaflets that exhibit reduced motion. This is in contradistinction to other causes of mitral regurgitation (e.g., dilated annulus, ruptured chordae) in which the regurgitant jet is eccentric and the valve is thin and hypermobile. The regurgitant volume can be determined from the difference between the total left ventricular stroke volume (estimated angiocardiographically) and the simultaneous measurement of the effective forward stroke volume by Fick's method.

One of the important objectives of cardiac catheterization in

patients with mitral insufficiency is the assessment of left ventricular function. The end-systolic indices, being unaffected by the loading conditions, are more reliable than ejection indices in assessing ventricular function in chronic mitral insufficiency.[11]

RHEUMATIC MITRAL STENOSIS

Stenosis of the mitral valve is usually secondary to rheumatic carditis. However, a number of other less common etiologies exist, such as congenital mitral stenosis, atrial myxoma, infective endocarditis with bulky vegetations, and mucopolysaccharidoses of the Hunter-Hurler phenotype.[29] The combination of mitral stenosis and secundum atrial septal defect is frequently referred to as Lutembacher's syndrome. In most cases, the mitral stenosis is rheumatic, and the association with atrial septal defect is fortuitous,[30] although the original report of mitral stenosis was felt to be the result of associated congenital cardiac malformations.

In patients with mitral stenosis, a history of rheumatic fever is obtained in only about two thirds of cases. In the remainder, the acute attack presumably escapes clinical recognition. It is still not clear whether the pathological changes seen in mitral stenosis are the result of subclinical rheumatic carditis or trauma produced by turbulent flow across a valve that has been deformed by the initial rheumatic process.

Pathology

Rheumatic fever causes mitral stenosis through fusion of the commissures, cusps, and/or chordae tendineae of the mitral valve apparatus. Commissural thickening and fusion make up the predominant lesion.

The stenosed mitral valve is typically funnel shaped, and the orifice is frequently shaped like a "fish mouth" or "buttonhole" (Fig. 87–5). Fibrosis is usually more marked at the periphery of the anterior cusp. The central part of the anterior cusp is less rigid and pliable. The opening snap and accentuated first heart sound characteristic of mitral stenosis are due to the up and down motions, respectively, of the central part of the anterior leaflet with ventricular diastole and systole. Calcium may be deposited in the valve leaflets, sometimes extending to involve the valve ring, and may become quite thick.[31] Occasionally, the thickened cusps may be so adherent to each other and pulled downward by the shortened chordae that they cannot open or close, thus reducing or abolishing the first sound and leading to combined mitral stenosis and insufficiency.

The left atrium is characteristically enlarged. Mural thrombosis may be present, most commonly involving the free wall just above the posterior cusp (MacCallum's patch). In long-standing cases, plaques of calcium may develop on the left atrial endocardial surface. Left atrial dilation may lead to elevation of the left main stem bronchus. The left ventricle is usually normal or reduced in size in pure mitral stenosis. Changes of pulmonary venous congestion, pulmonary hypertension, and hemosiderosis may develop in the lungs. It is usual to find dilation and hypertrophy of the right ventricle and functional tricuspid regurgitation.

Pathophysiology

Obstruction to flow across the narrowed mitral valve produces a diastolic gradient between the left atrium and the left ventricle. The left atrium–left ventricle diastolic gradient is related to the orifice size and the diastolic flow. The latter is determined by the cardiac output and by the duration of diastole. Serious circulatory disturbances with consequent clinical symptoms develop in adults when the area of the mitral opening is less than 1 cm^2. These data are not available for children. As narrowing proceeds, left atrial pressure increases, and blood stagnates in the pulmonary veins and capillaries, causing lung congestion (Fig. 87–6). Pulmonary arteriolar vasoconstriction occurs to protect the lungs against congestion. This occurs at the expense of developing pulmonary hypertension, which leads to right ventricular hypertrophy and eventually to right heart failure.

In the vast majority of patients with isolated mitral stenosis, the left ventricular end-diastolic volume is within the normal range. In a minority, it is below normal; and rarely, left ventricular volume is increased. Left ventricular contractility, as estimated

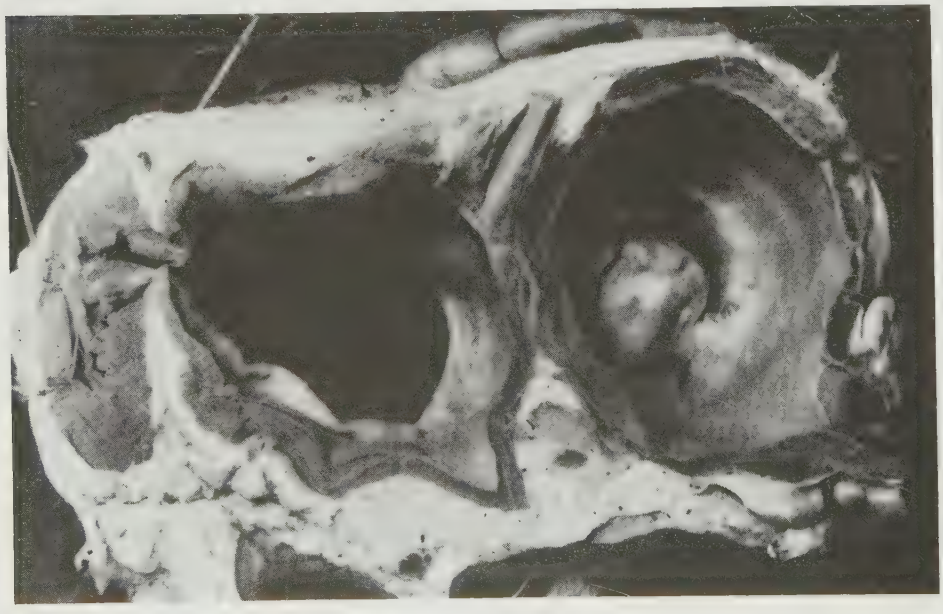

Fig. 87–5. Cross section specimen showing a stenosed mitral valve (on the right) giving a buttonhole appearance. The valve on the left is the tricuspid valve and is showing gross tricuspid insufficiency. The latter occurs in later stages of mitral stenosis because of the long-standing severe secondary pulmonary hypertension. (Courtesy of Dr. Soheir Mahfouz, Pathology Dept., Cairo University.)

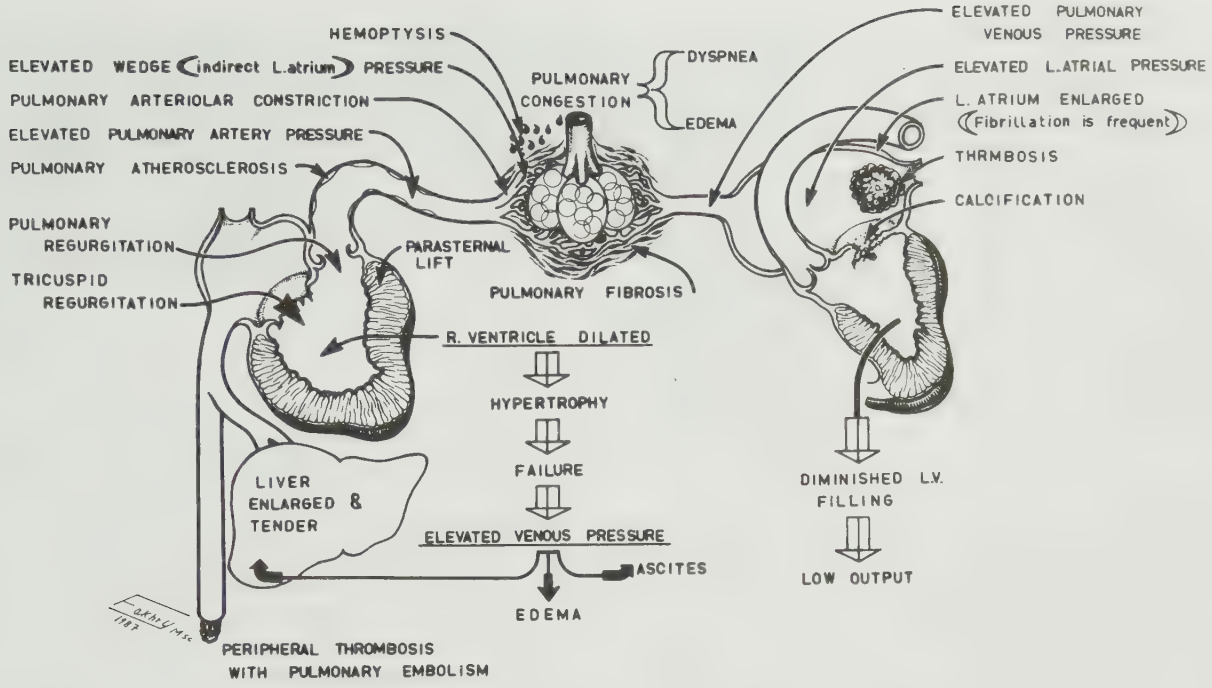

Fig. 87–6. A diagram depicting the hemodynamic alterations and complications that occur secondary to mitral stenosis.

by ejection phase indices, is within normal in the majority of patients. In approximately 30% of patients, left ventricular function is below normal, most likely owing to chronic reduction in preload and perhaps to the extension of the scarring process from the mitral valve into the adjacent posterobasal myocardium[32] or to low-level rheumatic carditis.

Fibrosis and disorganization of left atrial muscle bundles frequently occur in mitral stenosis as a result of the rheumatic process or as a consequence of left atrial dilatation caused by elevated left atrial pressure. Such changes lead to inhomogeneous conduction velocities and refractory periods and associated arrhythmias.

Symptoms

The symptoms of mitral stenosis may appear insidiously within three or four years after the attack of acute rheumatic fever. However, evidence of rheumatic mitral stenosis may be delayed up to 50 years. Some patients never develop symptoms. Sometimes the onset is abrupt, caused by the occurrence of a complication such as acute pulmonary edema, systemic embolism, or atrial fibrillation.

The symptoms depend upon the stage of the disease. Symptoms are absent in mild mitral stenosis. When pulmonary venous hypertension occurs, there is dyspnea, orthopnea, nocturnal dyspnea, recurrent chest infections, and hemoptysis. When pulmonary hypertension develops, symptoms caused by lung congestion diminish, and low cardiac output symptoms supervene. Symptoms caused by systemic congestion appear if the right ventricle fails.

General Examination

General examination reveals no abnormalities in mild cases. With the development of pulmonary hypertension, the face may show "malar flush,"[33] which is characterized by a cyanotic flush over the cheeks and dusky cyanosis of the lips partially caused by peripheral oxygen desaturation resulting from the low cardiac output. The jugular venous pulse shows a prominent a wave. The pulse is usually normal unless atrial fibrillation supervenes.

Precordial Examination

The apical impulse is felt at its site as a hurried slapping impulse. A characteristic diastolic or presystolic thrill ending in a palpable accentuated first sound is felt over the apex. When pulmonary hypertension develops, signs of enlargement of the pulmonary artery and hypertrophy of the right ventricle are detected. If right ventricular hypertrophy starts at a young age, a precordial bulge develops.

Auscultation

The first sound is loud, short, and snappy. The accentuation of the first sound is due to the open position of the cusps in the left ventricle at the end of diastole. This occurs because of the high pressure in and the continued emptying of the left atrium. The accentuation is also partly a result of the fibrotic changes in the cusps. The first sound loses its snappy character when calcification of the cusps supervenes. An opening snap, which is a sharp, clicky sound separated from the second sound by the isovolumic relaxation phase, may be present. The opening snap is caused by the sudden opening of the rigid mitral valve by the high left atrial pressure. The interval between the second sound and the opening snap decreases with increase in the degree of tightness, since increase of the left atrial pressure leads to early opening of the mitral valve.[34] The diastolic murmur of mitral stenosis is a low-pitched rumbling murmur that is best heard at the apex with the bell of the stethoscope. Although the intensity of the diastolic murmur is not closely related to the severity of the stenosis, the duration of the murmur is a guide to the degree of mitral obstruction. The murmur usually starts immediately after the mitral open-

ing snap. In mild cases, the murmur is brief. In severe stenosis, the murmur is holodiastolic with presystolic accentuation. Auscultation of the diastolic murmur of mitral stenosis is often facilitated by placing the patient in the left lateral position and listening during expiration after a few sit-ups. When pulmonary hypertension occurs, typical auscultatory phenomena appear, such as accentuated pulmonary second sound, narrow splitting of the second sound, and pulmonary ejection systolic click. There may be an ejection systolic murmur heard over the pulmonary artery from dilatation of the pulmonary artery. When dilatation of the pulmonary ring occurs, an early diastolic murmur of pulmonary insufficiency, Graham Steell's murmur, is heard. With severe pulmonary hypertension and decrease of blood flow across the mitral valve, the diastolic murmur of mitral stenosis again becomes shorter.

Electrocardiography

The electrocardiogram is normal in mild mitral stenosis. In patients with moderate or severe obstruction, the principal feature is left atrial enlargement (P-mitrale), which is demonstrated in 90% of patients with significant lesions.

The electrocardiographic signs of left atrial enlargement correlate more closely with left atrial volume than with left atrial pressure.[35] When atrial fibrillation supervenes, the fibrillatory waves are usually coarse (greater than 0.1 mV in amplitude in lead V_1), also suggesting the presence of atrial enlargement.[36] Electrocardiographic evidence of right ventricular hypertrophy depends on the level of right ventricular systolic pressure (Fig. 87–7).

Radiography

Findings depend on the severity of the disease. The cardiac silhouette may be normal in mild cases. In patients with hemodynamically significant mitral stenosis, left atrial enlargement is almost invariably evident on the lateral and right anterior oblique views (Fig. 87–8). The size of the left atrium does not correlate with the severity of the obstruction. Enlargement of the pulmonary artery, right ventricle, and right atrium is usual in mitral stenosis, depending on the severity of the disease (Fig. 87–9). Occasional calcification of the mitral valve is evident.

With chronic pulmonary venous hypertension, there is not only prominence of the pulmonary veins but also a redistribution of the flow toward the apices of the lungs. Interstitial edema is an indication of severe obstruction with pulmonary capillary pressure exceeding the oncotic pressure of the plasma protein (20 to 25 mm Hg). Kerley B lines are dense, short, horizontal lines most commonly seen at the costophrenic angles[37] that are thought to represent dilated pulmonary lymphatics.

Echocardiography

M-Mode Echocardiography

The M-mode echocardiographic criteria for the diagnosis of mitral stenosis include a reduced EF slope of the anterior mitral leaflet (Fig. 87–10). This finding is not highly specific. A reduced EF slope can be observed in patients with reduced left ventricular compliance. The EF slope is a function of the rate of filling of the left ventricle.[38] A poor correlation ($r = 0.41$) was detected between the degree of reduction of EF slope and the hemodynamically determined mitral valve area.

The posterior mitral leaflet moves parallel to the anterior mitral leaflet, so both leaflets move anteriorly in diastole. This results from commissural fusion and is considered the main diagnostic hallmark of mitral stenosis.[38] However, the posterior mitral leaflet can move posteriorly in patients with mild mitral stenosis.

Thickened mitral valve leaflets occur as a result of fibrosis and/or calcification. There can be decreased mitral valve excursion and separation of the two leaflets.

Two-Dimensional Echocardiography

The diagnostic feature of mitral stenosis in two-dimensional echocardiography (Fig. 87–11) is doming of the anterior leaflet in diastole; that is, the body of the leaflet separates more widely than the edges. The posterior leaflet is frequently stiff and appears severely restricted in diastolic movement. While M-mode echocardiography is of limited value in the quantification of the degree of stenosis in a given patient, an approximation of the severity

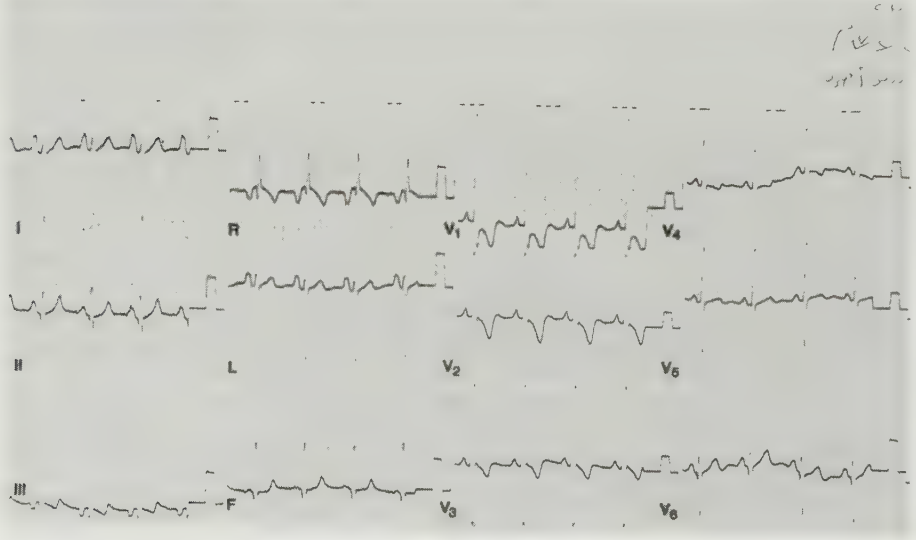

Fig. 87–7. An electrocardiogram from an advanced case of mitral stenosis with pulmonary hypertension, showing biatrial enlargement, right ventricular hypertrophy, and strain.

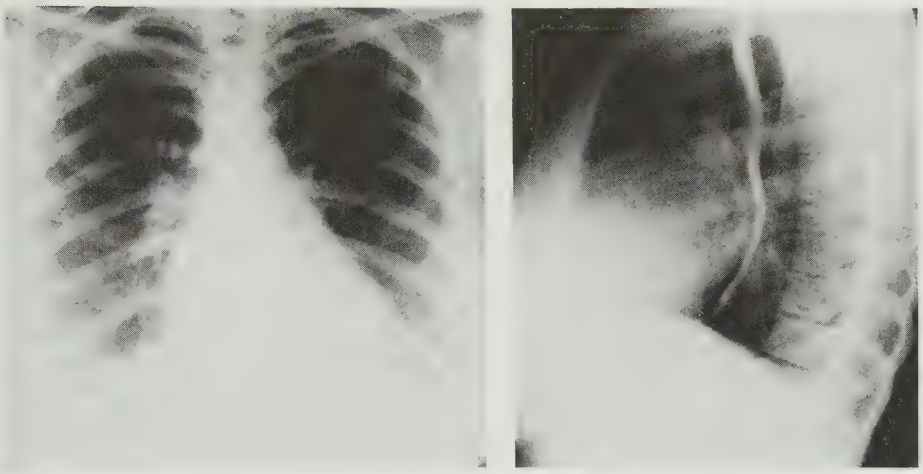

Fig. 87–8. Posteroanterior and lateral views from a patient with mitral stenosis showing mitralization of the heart, enlarged left atrium, and lung congestion.

can be achieved by two-dimensional echocardiography. Mitral valve area, in a short-axis view in diastole, can be measured by planimetry. The maximum diastolic separation of the edges of both leaflets in the long-axis view indicates the approximate severity of mitral stenosis and should be used in conjunction with a short-axis view for quantification. A favorable comparison of two-dimensional echocardiographically derived mitral valve area with mitral valve area measured directly at surgery has been reported by several authors.[19,39,40]

Orifice measurement at the *tip* of the funnel created by the opened mitral valve is required for accuracy. Scanning the mitral valve toward the base of the cusps (the area in which arching of the anterior leaflet occurs) results in underestimation of the severity of stenosis by echocardiography[19] and an orifice measurement that is larger than is really present.

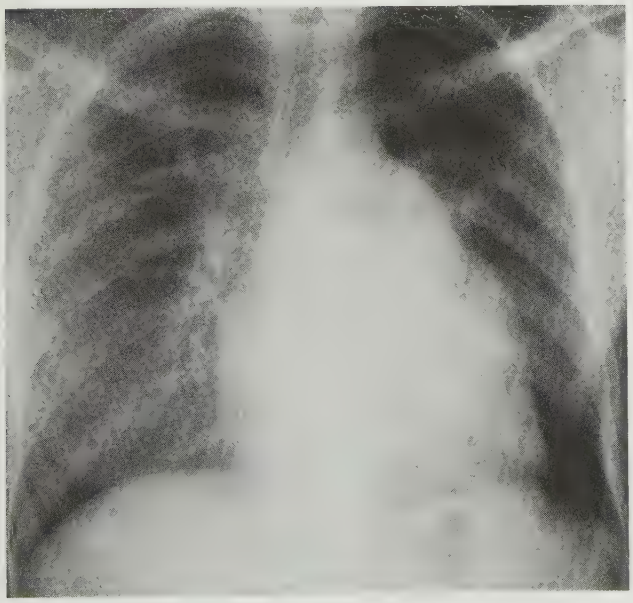

Fig. 87–9. Posteroanterior view from a patient with advanced mitral stenosis and pulmonary hypertension showing aneurysmal left atrium bulging on the left and right borders of the heart and enlarged pulmonary artery.

Doppler Echocardiography

Doppler echocardiography provides information about the flow of blood across the mitral valve and is useful in conjunction with two-dimensional echocardiography in evaluating mitral stenosis.

The Doppler flow profile of a normal mitral valve looks similar in configuration to the M-mode tracing with an early diastolic peak, a rapid fall, and a late diastolic peak. The velocity of the Doppler signal across the mitral valve reflects the pressure gradient between the left atrium and the left ventricle in diastole. The normal mitral valve peak velocity does not exceed 1.2 mm/s. In mitral stenosis, the diastolic velocity is higher and exceeds 1.5 mm/s. Also, the slower decline in the diastolic pressure gradient across the mitral valve results in a slower velocity drop during diastole. As the stenosis increases, the diastolic gradient increases for a longer time, and the negative descent of the diastolic Doppler velocity becomes slower.

There are two methods to estimate the severity of mitral stenosis from the Doppler signal. Instantaneous pressure drop (Δ P) between two chambers can be calculated from the Doppler velocity (V) by using a modified Bernoulli equation ($\Delta P = r \times V^2$). The mitral valve Doppler tracing can be used to determine both mean and instantaneous pressure gradients across the mitral valve. The correlation between simultaneous cardiac catheterization and pressure gradients calculated from Doppler echocardiography is excellent.[13–19,41–45] The second method for quantification of the severity of mitral stenosis uses diastolic half-time ($t\frac{1}{2}$). As the stenosis becomes more severe, the decline in pressure gradient during the diastole of the cardiac cycle between left atrium and left ventricle is slower. The rate of decline can be measured by the "$t\frac{1}{2}$," which is the time it takes for the velocity to decrease to 50%. This is an accurate measurement of the severity of mitral stenosis. The diastolic pressure half-time is inversely proportional to the mitral valve area and is independent of heart rate, coexistent mitral insufficiency, or atrial fibrillation. Normally, $t\frac{1}{2}$ is 20 to 60 ms. In mitral stenosis, it reaches 90 to >300 ms. Hatle and associates[46] found that by dividing 220 by the $t\frac{1}{2}$, a value for the mitral valve area could be obtained directly. Measurement of the diastolic $t\frac{1}{2}$ by Doppler echocardiography is highly accurate in comparison with cardiac catheterization measurements.[17–19]

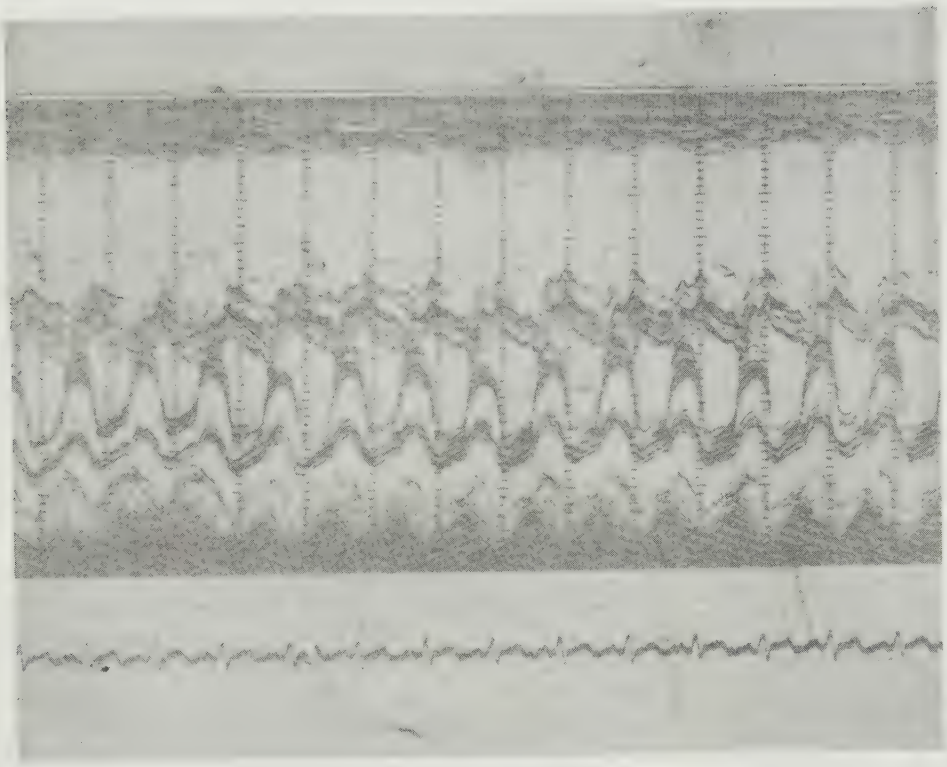

Fig. 87–10. M-mode echocardiogram from a patient with mitral stenosis showing slow EF slope, thickened mitral leaflets, and concordant movement of the anterior and posterior leaflets. The right ventricle is enlarged, indicating the presence of pulmonary hypertension.

Cardiac Catheterization and Angiography

Cardiac catheterization and angiography are not usually necessary in isolated mitral stenosis but may still be performed in atypical cases. In patients with mild severity by noninvasive assessment but significant symptoms, cardiac catheterization might be needed. The characteristic findings at catheterization include elevated left atrial and pulmonary capillary wedge pressures. In patients with sinus rhythm, the left atrial pressure pulse often exhibits a prominent atrial contraction a wave and a gradual pressure decline after mitral valve opening Y descent; the mean left atrial pressure is elevated (Fig. 87–12). In patients with mild-to-moderate stenosis without elevation of pulmonary vascular resistance, pulmonary artery pressure may be normal at rest and rise only during exercise. However, in patients with severe stenosis

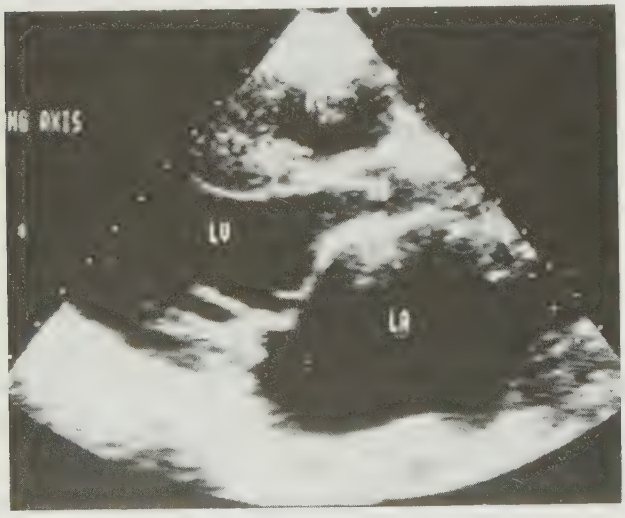

Fig. 87–11. Two-dimensional echocardiogram from a patient with mitral stenosis showing incomplete opening of the mitral valve. The anterior leaflet is doming, while the posterior leaflet is restricted. The left atrium (LA) is markedly enlarged. LV = left ventricle; RV = right ventricle; AO = aorta.

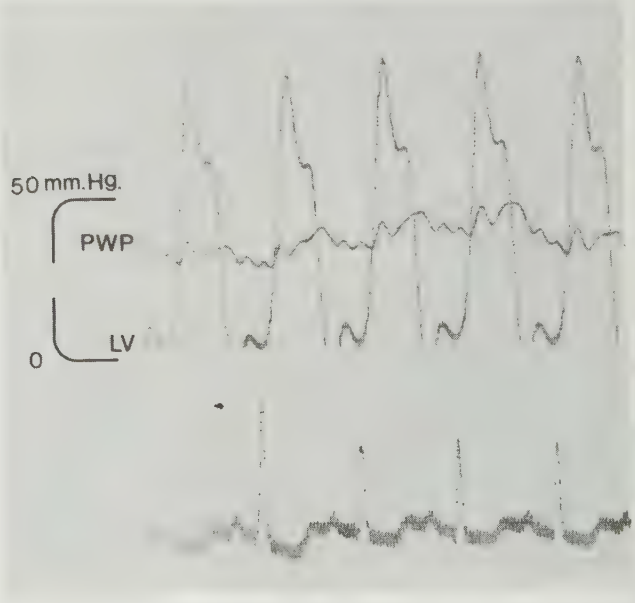

Fig. 87–12. Simultaneous left ventricular (LV) and pulmonary capillary wedge (PWP) pressures from a patient with mitral stenosis showing significant diastolic gradient across the mitral valve.

and those in whom the pulmonary vascular resistance is significantly increased, pulmonary arterial pressure is elevated at rest.

If mitral stenosis is of indeterminate severity, it is extremely important to exercise the patient because a small difference between the left ventricular end-diastolic pressure and the left atrial pressure can increase markedly during exercise, particularly when the resting cardiac output is low. Consequently, what seems to be only mild stenosis at rest as judged by the resting gradient clearly becomes severe stenosis when exercise is performed.

Diagnosis

The diagnosis of mitral stenosis is usually straightforward on the basis of history, physical signs, and chest roentgenogram and can be rapidly confirmed by echocardiography. An attempt should be made to quantify the severity of the mitral stenosis as well as to diagnose its presence. Quite reliably, this can be achieved from the history, the length of the diastolic murmur, the presence and severity of pulmonary hypertension, and right ventricular hypertrophy. Measurement of the mitral diastolic pressure gradient or the valve area at cardiac catheterization allows the obstruction to blood flow to be quantitated, and it is also possible to measure the left ventricular filling pattern either by echocardiography or by Doppler methods that give similar information. With limitations, valve area can be assessed directly by planimetry using two-dimensional echocardiography and indirectly by Doppler methods using pressure half-time measurements.

There are several conditions that may mimic mitral stenosis. These include left atrial myxoma, cor triatriatum, pulmonary veno-occlusive disease, and Austin Flint murmur from aortic regurgitation.

Left Atrial Myxoma

Left atrial myxoma may mimic all the physical signs of mitral stenosis including mid-diastolic and presystolic murmurs, loud first sound, and an opening snap known as a "tumor plop." It may lead to dyspnea and to systemic embolization. Variable murmurs are often described; however, constant murmurs or a total absence of auscultatory abnormalities is equally characteristic. Echocardiography is diagnostic and shows a characteristic mass of echoes behind the mitral valve during diastole. Atrial myxoma is less common in series of pediatric cardiac tumor cases than in adult cardiac tumor series, as is discussed in Chapter 96.

Cor Triatriatum

The congenital anomaly cor triatriatum may lead to obstruction of blood flow at the atrial level and may mimic mitral stenosis, particularly in childhood. Elevations of both pulmonary venous pressure and pulmonary vascular resistance result in severe pulmonary artery hypertension. The diagnosis should be suspected at cardiac catheterization if the pulmonary artery wedge pressure is higher than a simultaneous left atrial pressure. The diagnosis is established by visualizing the obstructing lesion echocardiographically or angiographically. A more complete discussion may be found in Chapter 77.

Pulmonary Veno-Occlusive Disease

Pulmonary veno-occlusive disease is an extremely rare condition of unknown etiology that has been reported in infants, children, and occasionally adults. In this disease, one finds intimal fibrosis affecting pulmonary veins of all sizes. Individual veins may show concentric or eccentric narrowing or complete occlusion. The appearances of these veins suggest recanalization following organization of thrombus. Pulmonary venous hypertension results in pulmonary arterial hypertension and right ventricular hypertrophy. This condition may stimulate silent mitral stenosis, but there is no left atrial enlargement. Because the condition may be patchy, pulmonary artery wedge pressure may be high or low according to whether the catheter is wedged in an affected or unaffected segment of the lung. Lung biopsy may be required in establishing this diagnosis.

Austin Flint Murmur from Aortic Regurgitation

In the presence of severe aortic regurgitation, a mid-diastolic murmur may be audible at the cardiac apex in the absence of organic mitral valve disease. This murmur can be presystolic rather than mid-diastolic on occasion. The murmur is the result of fluttering of the anterior leaflet of the mitral valve caused by the regurgitant stream. On clinical grounds, this murmur may sometimes be differentiated from coexistent mitral stenosis by the fact that, in the Austin Flint murmur, the first sound is never palpable, and an opening snap is never present. Echocardiography and Doppler examination are usually required for certainty.

LUTEMBACHER'S SYNDROME

Patients with rheumatic mitral stenosis may have associated atrial septal defect, a combination known as Lutembacher's syndrome.[30] The combination is still seen in areas where rheumatic heart disease is prevalent.

The atrial septal defect exerts a protective effect on the lungs in mitral stenosis by decompressing the left atrium. However, the high left atrial pressure secondary to mitral stenosis exaggerates the left-to-right shunt across the atrial septal defect with its consequences on the lungs.

Patients are virtually always symptomatic from increased lung flow, liver congestion, and low cardiac output. However, "cardiac asthma" and orthopnea do not occur. The findings on examination suggest both lesions. Errors may occur in diagnosis. A patient with both lesions may be thought to have mitral stenosis or atrial septal defect. Constant splitting of the second sound with mitral stenosis indicates associated atrial septal defect. An electrocardiogram with an RSR′ pattern in the right chest leads (Fig. 87–13), or a chest roentgenogram with a markedly enlarged pulmonary artery and plethoric lungs (Fig. 87–14) in a patient with mitral stenosis, should suggest associated atrial septal defect. Echocardiography is very helpful (Fig. 87–15), since it can show both lesions. Cardiac catheterization reveals excessive pulmonary flow. The gradient across the stenotic mitral valve is usually small or absent with large atrial septal defect and diagnosis depends on angiography (Figs. 87–16, 87–17).

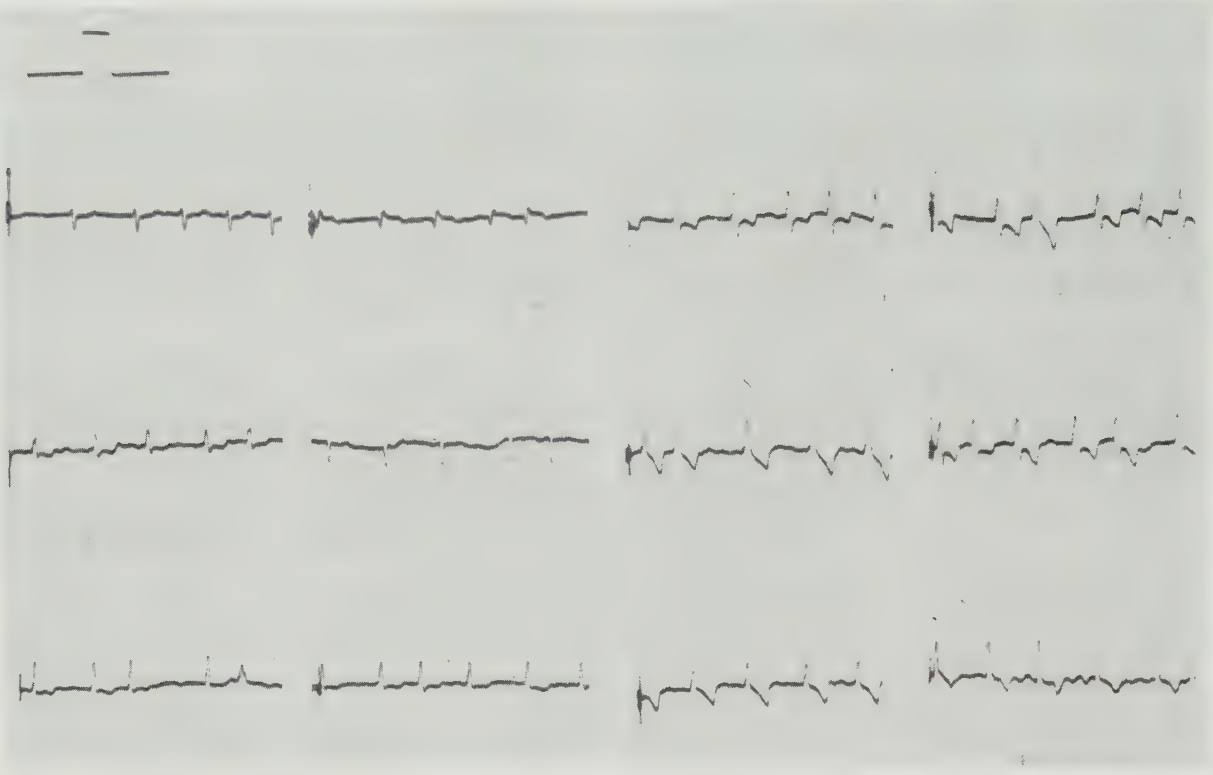

Fig. 87–13. The presence of rSR in V_1 in this patient with the clinical diagnosis of mitral stenosis suggested additional atrial septal defect. The patient also had atrial fibrillation.

AORTIC VALVE DISEASE

Aortic valvulitis, which may develop during rheumatic carditis, may cause aortic insufficiency and/or stenosis. Insufficiency, which results from damage of the aortic leaflets, occurs early in the course of the disease and may be exaggerated by time because of fibrosis, thickening, and contracture of the aortic leaflets (Fig. 87–18). Stenosis resulting from fusion of the commissures takes a long time to develop. As a result, aortic valve disease of rheumatic etiology in children and adolescents usually presents as isolated or dominant insufficiency with mild or no stenosis. Dominant stenosis with or without insufficiency at a young age is usually congenital. A rheumatic aortic valve has a characteristic appearance of a tricuspid valve with thickened cusps, rolled edges, and fused commissures.

Pathophysiology

The inability of the shortened aortic leaflets to coapt and close the aortic orifice completely during ventricular diastole causes diastolic regurgitation of blood from the aorta to the left ventricle (Fig. 87–19). Since the normal aortic diastolic pressure approximates 80 mm Hg and the normal left ventricular diastolic pressure is 0 to 12 mm Hg, any degree of aortic insufficiency may lead to significant regurgitation. A regurgitant area of approximately 20% of the aortic orifice area can double total left ventricular output and left ventricular work.[47] With severe aortic insufficiency, the

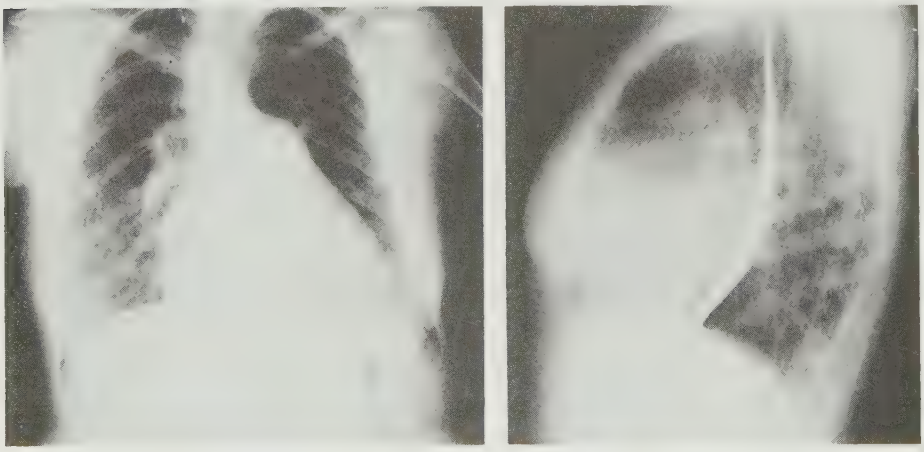

Fig. 87–14. Posteroanterior and lateral views from the patient of Fig. 87–13. The enlarged pulmonary artery and lung plethora also suggest associated atrial septal defect. The left atrium is slightly enlarged.

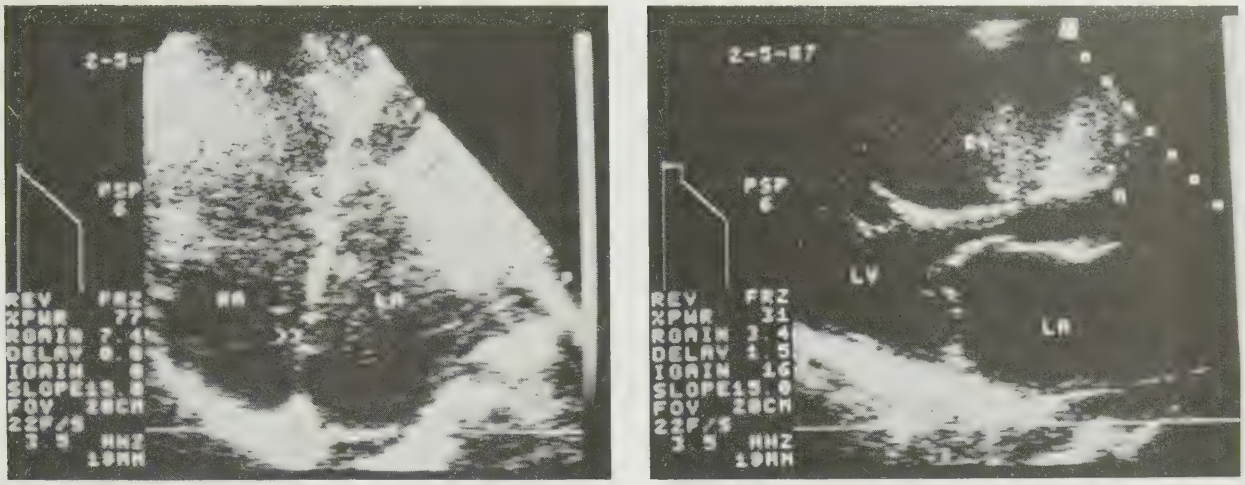

Fig. 87–15. Two-dimensional echocardiogram from the patient of Fig. 87–13. The right section is a longitudinal one showing mitral stenosis and the left is a subcostal view, confirming the presence of associated secundum atrial septal defect. RA = right atrium; RV = right ventricle; LA = left atrium; A = aorta.

diastolic leak into the left ventricle may be as high as 60% or more of the left ventricular stroke volume.[48]

With chronic aortic insufficiency, the left ventricle dilates and accommodates more blood for many years. The increase in left ventricular diastolic volume is not accompanied by an increase in end-diastolic pressure probably because of an increase in the left ventricular diastolic compliance. The increase in left ventricular end-diastolic volume encroaches on preload reserve and, according to Starling's law, increases stroke volume.[49,50] This compensatory mechanism is aided by reduced aortic impedance (and therefore afterload), which occurs because of reflex peripheral vasodilation. Another compensatory mechanism is eccentric left ventricular hypertrophy, which tends to normalize left ventricular wall stress as described by Laplace's law ($0 = Pa/2h$, where 0 is circumferential wall stress, P is intraventricular pressure, a is intraventricular radius, and h is wall thickness).[51,52]

Increase of left ventricular stroke volume with consequent elevation of the systolic blood pressure accompanied by decrease of the diastolic blood pressure (caused partly by regurgitation of a part of the stroke volume and partly by peripheral arteriolar vasodilation) leads to an increase in the pulse pressure. The classic peripheral arterial pulses of aortic insufficiency show a rapid rise to a high peak with a collapsing descending limb, an insignificant dicrotic notch, and a low diastolic pressure.[53]

Myocardial oxygen consumption increases with aortic insufficiency caused by increase of preload, left ventricular wall tension, and left ventricular mass. Since the major portion of coronary flow occurs during diastole, when arterial pressure is lower than normal, coronary perfusion is reduced,[54] and the increased oxygen demand and reduced coronary flow may lead to myocardial ischemia, especially with exercise.[55]

Exhaustion of the compensatory mechanisms (preload reserve, increased contractility, and diminished afterload) as well as myocardial ischemia may result in left ventricular failure. Because significant cardiac compensation is related to an increased ejection fraction, a "normal" ejection fraction suggests inadequate compensation in response to the regurgitation.[56] Decreased ejection fraction leads to increased end-systolic volume, which in turn

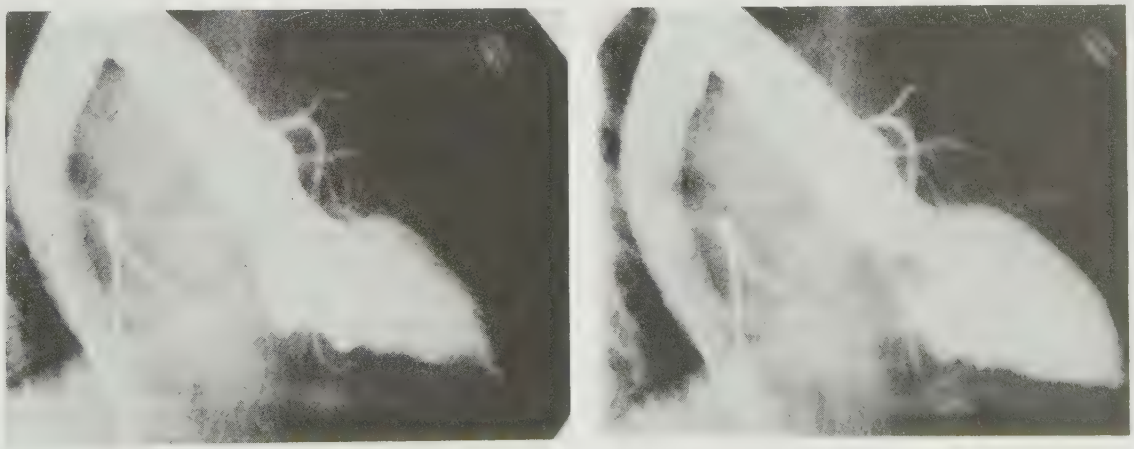

Fig. 87–16. Systolic and diastolic left ventricular angiogram from the patient of Fig. 87–13 in right anterior oblique, showing restricted mitral valve movement diagnostic of mitral stenosis.

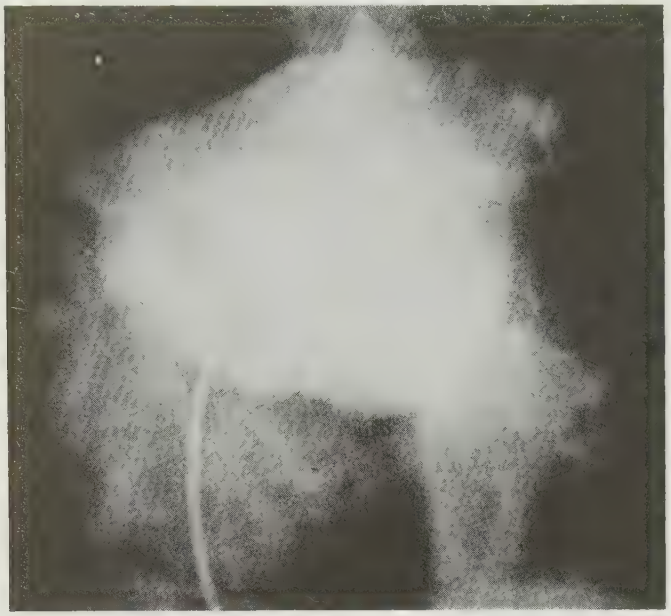

Fig. 87–17. Right upper pulmonary vein angiogram from the patient of Fig. 87–13 showing the funnel-shaped mitral valve (inverted dome) and the radiopaque blood passing from the left atrium to the right atrium through the atrial septal defect.

Fig. 87–18. Gross left ventricular dilatation and hypertrophy secondary to rheumatic aortic insufficiency. (Courtesy of Dr. Soheir Mahfouz, Pathology Dept., Cairo University.)

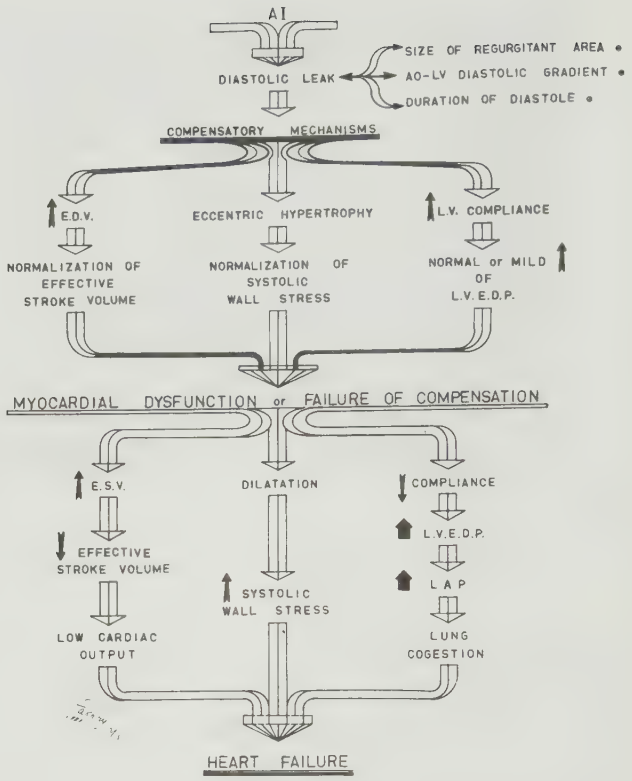

Fig. 87–19. A diagram depicting factors that determine the amount of regurgitation, compensation, and decompensation in aortic insufficiency.

appears to be one of the most sensitive indices of myocardial dysfunction.[57] Ultimately, left ventricular end-diastolic pressure starts to rise. Levels as high as 60 mm Hg have been reported[58] and may equal the aortic diastolic pressure. Patients with severe aortic insufficiency have the largest left ventricular diastolic volumes of any form of heart disease.

With rise of left ventricular diastolic pressure, the magnitude of the aortic leak decreases with concomitant elevation of diastolic aortic pressure, reduction of the aortic insufficiency murmur, and reduction of peripheral signs. In some patients with this defect, the left ventricular diastolic pressure exceeds that in the left atrium in mid-diastole with consequent premature closure of the mitral valve.

In chronic aortic insufficiency, many of these compensatory and decompensatory changes occur before the onset of symptoms. The symptoms usually start only when the high left ventricular end-diastolic pressure is reflected on the left atrial and pulmonary capillary pressures. Progressive left ventricular dilatation may result in second mitral insufficiency, which leads to a rapid downhill course.

End-systolic indices (e.g., end-systolic pressure, volume, or stress volume relations) appear to be independent of the loading conditions and have proved to be superior to isovolumic (dp/dt, etc.) and ejection phase (fractional shortening, ejection fraction) indices in detecting early left ventricular dysfunction in individual cases.[11]

Associated aortic stenosis causes significant deleterious alterations in the pathophysiology. The increased stroke volume pro-

duced by aortic insufficiency causes a corresponding increase in the pressure gradient across the stenotic valve. At the same time, the decreased compliance of the left ventricle secondary to hypertrophy produced by the aortic stenosis leads to the inability of the left ventricle to accommodate the regurgitant blood of aortic insufficiency.

Symptoms

Early symptoms are unusual except with gross aortic insufficiency.

Patients may complain of cardiac awareness especially with exercise because of the large stroke volume and forceful left ventricular contractions. Those with severe aortic insufficiency may occasionally feel pain along the carotid arteries or even the abdominal aorta because of exaggerated pulsations of these arteries.[59] Excessive sweating and heat intolerance due to vasodilatation may be an early symptom. Chest pain may be a prominent symptom during exertion. Disturbing anginal pains may occur by night accompanied by tachycardia, sweating, and paroxysmal hypertension.

However, the main symptoms are caused by left ventricular decompensation, breathlessness being the most prominent symptom. Symptoms usually start on exertion, but nocturnal dyspnea or even an attack of acute pulmonary edema precipitated by severe exertion may be the presenting symptom.

Sudden death may occur in patients with uncontrollable angina, nocturnal angina, severe heart failure, and most commonly in patients with frequent ventricular arrhythmias.

Symptoms are exaggerated and occur earlier if aortic insufficiency is associated with aortic stenosis.

General Examination

The characteristic peripheral signs of aortic insufficiency are produced by the combined large pulse volume and peripheral vasodilation. The sharp rise of the pulse gives it a characteristic "water hammer" quality. The visible jerky arterial pulsations in the neck are known as Corrigan's sign. Nodding of the head with the strong heart beats is known as de Musset's sign. Duroziez's sign is elicited by compression of the femoral pulse and listening proximally for a diastolic murmur with the stethoscope. This implies retrograde flow in the femoral artery caused by aortic regurgitation of at least moderate severity. A systolic murmur elicited by this technique is heard normally and does not indicate the presence of aortic regurgitation. Capillary nailbed pulsations and exaggerated retinal artery pulsations can be elicited in severe aortic insufficiency.

The character of the pulse is modified in mixed aortic valve disease. With aortic stenosis, there is diminution of the pulse volume and a detectable notch halfway up the stroke. Pulsus bisferiens, which was previously considered to be associated with combined stenosis and insufficiency, is not an uncommon finding in pure aortic insufficiency.

The blood pressure is normal only in very mild aortic insufficiency. With increasing severity, the systolic pressure rises while the diastolic pressure falls. Indirect estimation of the diastolic pressure in severe aortic insufficiency is difficult because "pistol sounds" may be heard over the brachial artery without any pressure being applied by the cuff. This gives a false impression of a diastolic pressure of zero. In such patients, it is better to record the pressure at which sounds become muffled as well as the pressure at which they disappear. A reading of 160/40–0 is more appropriate than a reading of 160/0. The direct intra-arterial diastolic pressure is seldom below 40 mm Hg.[60] With a rise in left ventricular diastolic pressure, the magnitude of the aortic leak is reduced, as was explained. Hence some patients with gross aortic insufficiency may have a diastolic pressure of 60 mm Hg or more, especially when heart failure is complicated by peripheral vasoconstriction.

The venous pressure and waves are usually normal until late in the disease, unless a Bernheim a wave is produced. This is caused by the ventricular septum bulging to the right, thus retarding filling of the right ventricle.

Precordial Examination

The apical impulse in aortic valve disease is diffuse and hyperdynamic and may be displaced laterally and inferiorly. With severe aortic insufficiency, there is often a palpable apical diastolic thrust coincident with a left ventricular diastolic gallop.

A systolic thrill over the aortic area, which was thought to indicate the association of aortic stenosis, can be felt in severe isolated aortic insufficiency caused by increased left ventricular stroke output coupled with dilatation of the aortic root.

Auscultation

Heart sounds are normal in isolated aortic insufficiency. The aortic component of the second sound is weak if there is associated aortic stenosis.

The typical murmur of aortic insufficiency is an early diastolic high-pitched blowing decrescendo murmur over the base, which begins with the second sound. In rheumatic patients, the murmur is maximally heard parasternally over the second and third left intercostal spaces and may be propagated down to the apex. It is best heard with the diaphragm of the stethoscope while the patient is sitting and leaning forward in full expiration. The duration, rather than the quality or loudness of the aortic diastolic murmur, correlates with the severity of the aortic insufficiency. The aortic insufficiency murmur tends to decrease or disappear during pregnancy and to increase if the systemic resistance is elevated as by phenylephrine. When heart failure supervenes and the left ventricular diastolic pressure increases with consequent decrease of regurgitation, the intensity and duration of the aortic insufficiency murmur decrease or disappear completely.

An ejection systolic murmur at the base is heard in almost all cases of aortic insufficiency of more than mild degree because of increased blood flowing across the aortic valve in systole. The diagnosis of associated aortic stenosis cannot be made merely from the presence of this systolic murmur, since it may reach up to grade IV/VI with isolated significant aortic insufficiency.

A mid-diastolic or presystolic rumble over the mitral area, the Austin Flint murmur, is usually heard in patients with moderate or severe aortic insufficiency without associated organic mitral stenosis.[61] The Austin Flint murmur may be due to relative mitral stenosis secondary to improper opening of the anterior leaflet of the mitral valve either by the regurgitant bloodstream or by the high left ventricular diastolic pressure.[62] The Austin Flint murmur can also be caused by the addition of a diastolic or presystolic gallop to the aortic insufficiency murmur.[63] The Austin Flint murmur disappears lateral to the area of ventricular gallop. The Austin

Flint murmur usually occurs with left ventricular hypertrophy and with diastolic blood pressure of 60 mm Hg or less and is not accompanied by the opening snap or the accentuated first sound of organic mitral stenosis. Amyl nitrite decreases the Austin Flint murmur by decreasing systemic resistance but increases the mitral stenosis murmur because of tachycardia and increased cardiac output. The Austin Flint murmur is not accompanied by electrocardiogram, radiological, or echocardiogram manifestations of organic mitral stenosis. Echocardiography is now the most sensitive way of differentiation between an Austin Flint and an organic apical diastolic murmur.

Electrocardiography

The electrocardiogram is normal in mild and sometimes in severe aortic valve disease; 20% of operative candidates at Massachusetts General Hospital had no left ventricular hypertrophy by voltage criteria.[64] However, in most severe cases, left ventricular hypertrophy develops on the electrocardiogram. The changes at first consist mainly of increased QRS voltage in the left precordial leads. The T wave may be tall and upright at first; but later on, ST and T wave changes characteristic of strain develop[65,66] (Fig. 87–20). Left bundle branch block may appear in advanced cases. P wave changes of left atrial enlargement appear when left ventricular failure develops. Atrial fibrillation is rare in isolated aortic valve disease without mitral valve disease.

Radiography

In chronic aortic insufficiency, the chest radiograph provides more information than the electrocardiogram. As severity of aortic insufficiency increases, there is more dilatation and enlargement of the left ventricle. Typically, the left ventricle enlarges in an inferior and leftward direction and can be seen below the diaphragmatic level. The cardiothoracic ratio is related to the duration and severity of aortic insufficiency and consequently has value in predicting the outcome of surgical treatment.[62] Patients with a cardiothoracic ratio exceeding 0.64 have a postoperative death rate of 30% in contrast to 7% in patients with less cardiac enlargement.[67] The aortic root is usually dilated. Pulmonary venous congestion and generalized cardiac enlargement are seen when cardiac failure develops.

Echocardiography

The most common and characteristic M-mode echocardiographic finding in chronic aortic insufficiency is fine diastolic fluttering of the mitral valve, more frequently the anterior leaflet[68] (Fig. 87–21). Mitral valve fluttering, however, is not specific for aortic insufficiency[69] and may be absent in some patients, especially if mitral stenosis is also present. The sensitivity of this echocardiographic feature fell from 72% in isolated lesions to 40% when mitral stenosis was also present.[19]

Two-dimensional echocardiography is less useful than M-mode echocardiography in the recognition of chronic aortic insufficiency. However, it is more useful in identifying the etiology.

Reversed diastolic doming of the anterior mitral leaflet was detected by two-dimensional echocardiography in 19 of 22 patients[70] with moderately severe aortic insufficiency and in 13 of 25 patients[19] with severe aortic insufficiency and was not seen in normal subjects.

Apart from its diagnostic capabilities, echocardiography has an important role in the clinical assessment and in the evaluation of changes in left ventricular function in patients suffering from aortic insufficiency. In a serial echocardiographic study of patients with asymptomatic aortic insufficiency, Henry and associates[71] reported in 1980 that early left ventricular failure was more likely to occur when the end-systolic left ventricular dimension exceeded 55 mm or when the percent fractional shortening was less than 25%. Similar results were obtained in 1978 by Bonow and co-workers,[72] who showed that late deaths due to heart failure after aortic valve replacement occurred in patients with echocardiographically determined ejection fraction of 63% or less and left ventricular systolic dimension of 53 mm or more. Gaasch and associates[73] demonstrated in 1983 that patients with aortic insufficiency whose left ventricular end-diastolic diameter was more than 3.8 cm/m^2 were at risk of persistent postoperative left ventricular enlargement and reduced survival. On the basis of these studies, it was recommended that patients with asymptomatic aortic insufficiency and left ventricular end-systolic diameter of 50 mm be examined once

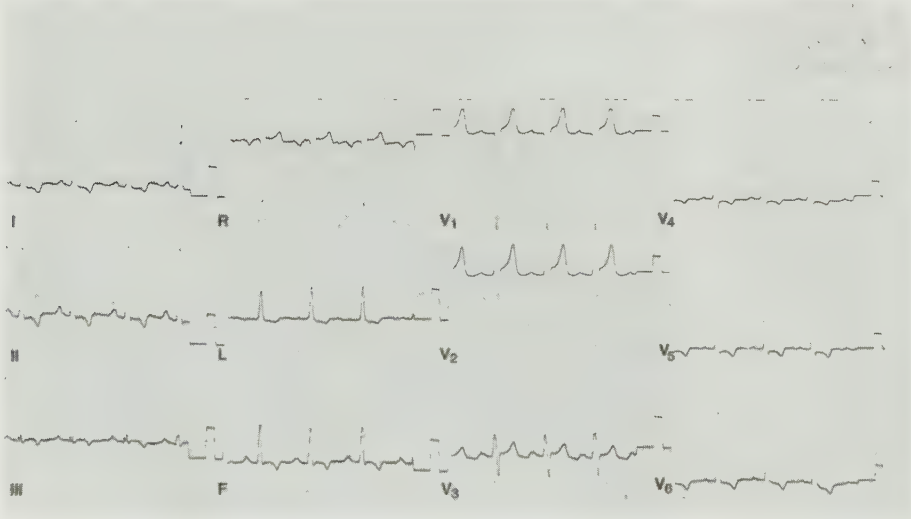

Fig. 87–20. An electrocardiogram showing severe left ventricular hypertrophy and strain from a patient with gross aortic insufficiency.

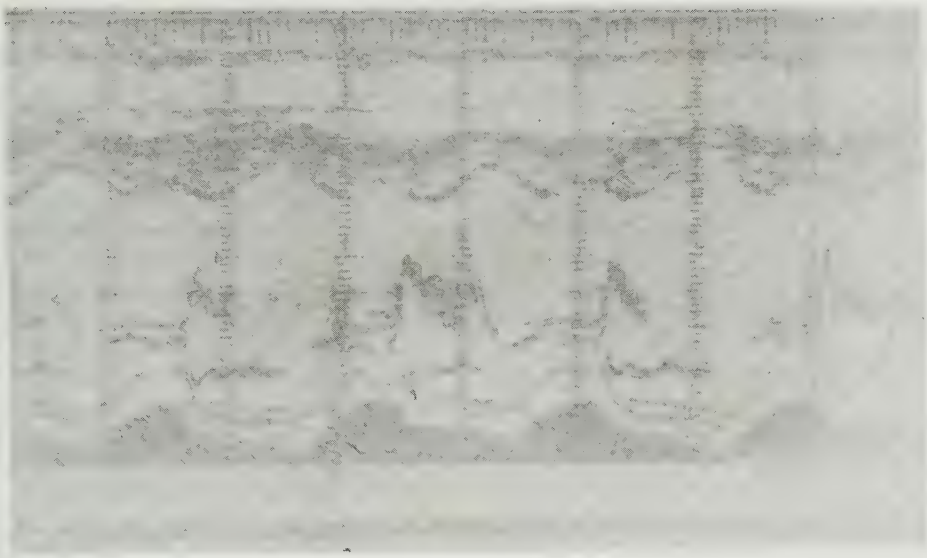

Fig. 87–21. M-mode echocardiogram showing fluttering of the anterior leaflet of the mitral valve caused by aortic insufficiency.

a year, patients with end-systolic diameter of 50 to 54 mm be examined once every four to six months, and aortic valve replacement be considered in asymptomatic patients with aortic insufficiency in which end-systolic diameter is greater than 55 mm. Later, studies by Fioretti and co-workers[74] in 1983 and Daniel and co-workers[75] in 1985 reported that both end-systolic diameter and end-diastolic diameter decreased postoperatively with long-term survival in patients who underwent aortic valve replacement for symptomatic aortic insufficiency who had preoperative end-systolic diameter greater than 55 mm. Patients who did not show marked decrease in end-diastolic diameter (by at least 11 mm) in the early postoperative period after aortic valve replacement seemed to have severe myocardial damage, and their prognosis was guarded.[76]

Other echocardiographic assessments of global function are based on estimates of left ventricular systolic wall stress (e.g., end-systolic wall stress or radius-to-thickness ratio).

Serial echocardiographic studies can detect early changes in left ventricular function. Deterioration is indicated if there is progressive increase in end-systolic and end-diastolic dimensions with gradual reduction of left ventricular shortening and ejection.

Doppler is the most sensitive noninvasive method of detecting aortic insufficiency. The diagnostic sensitivity of aortic insufficiency by Doppler ranged from 90%[19] to 97%.[77] The false-negative diagnoses of aortic insufficiency were encountered only in patients with angiographically mild insufficiency. This significantly high sensitivity has been reported in isolated lesions as well as in patients with associated mitral stenosis in whom echocardiography has proved less sensitive. Doppler has also proved satisfactorily specific in detecting aortic insufficiency. It showed a specificity of 92 to 100%.[19,78]

Accurate evaluation of the severity of aortic insufficiency by Doppler has not so far been satisfactorily achieved. However, several techniques for semiquantitative assessment of the severity of aortic insufficiency have been performed. Doppler echocardiographic measurement of the aortic regurgitant fraction has been performed by (1) comparing the forward and reverse flows in the aortic arch,[79] (2) comparing the systolic aortic and pulmonary volume flows,[80] (3) comparing the transmitral volumetric flow and the left ventricular total stroke volume, (4) measuring the extent of the regurgitant jet into the left ventricular outflow tract,[19,81] and (5) measuring the mitral pressure half-time.[82]

Color Doppler flow mapping of the regurgitant jet of aortic insufficiency offers a more precise approach to quantitating the severity of the leak.[83,84]

Cardiac Catheterization and Angiography

As has been discussed, left ventricular pressures are normal in aortic insufficiency until late in the disease. With left ventricular failure, there is elevation of left ventricular end-diastolic pressure with secondary elevation of left atrial and pulmonary capillary wedge pressures (Fig. 87–8). Associated aortic stenosis and/or mitral stenosis can be excluded by lack of gradients across the aortic and mitral valves.

Aortography (Fig. 87–9) is important to diagnose aortic insufficiency and grade its severity. There are four grades of quantification. One-plus represents a faint puff of regurgitation into the left ventricle. Two-plus indicates more regurgitation, which does not completely fill the ventricle. Three-plus indicates opacification of the entire left ventricle. Four-plus is applied if the opacification in the left ventricle equals that in the aorta.

Left ventriculography is an integral part of angiography for aortic insufficiency. It is helpful in determining the size of the left ventricle and the presence and degree of associated mitral regurgitation as well as in studying left ventricular function.

Course and Prognosis

Mild and moderate lesions are well tolerated for a long time.[85] Recurrence of rheumatic activity or the development of infective endocarditis initiates a rapid downhill progressive course. Severe aortic insufficiency may be tolerated for variable times, but patients will eventually be symptomatic because of the development of congestive failure as well as angina. Sudden death may occur. Signs of a poor prognosis include severe aortic valve disease, resistant anginal pains, resistant left ventricular failure, and frequent ventricular arrhythmias.

Diagnosis and Differential Diagnosis

The diagnosis of aortic insufficiency is usually not difficult if the characteristic murmur is detected. The most common reason for missing the diagnosis is failure to perform a careful, systematic examination in a quiet atmosphere. Once the characteristic murmur is heard, it has to be differentiated from other causes of left parasternal diastolic murmurs such as Graham Steell's murmur. The latter is a soft early diastolic left parasternal murmur resulting from functional pulmonary incompetence secondary to dilatation of the pulmonary artery as a result of severe pulmonary hypertension. If the systemic arterial pulse pressure is wide and the diastolic pressure is low, aortic insufficiency is likely to be the cause of the murmur. The murmur of pulmonary insufficiency is usually not heard to the right of the sternum, whereas the murmur of aortic insufficiency, although louder to the left of the sternum, is usually well heard also to the right. Graham Steell's murmur is associated with the clinical and laboratory manifestations of pulmonary hypertension. Doppler echocardiography is a very sensitive tool in differentiation between pulmonary and aortic insufficiency.

Aortic insufficiency also has to be differentiated from other causes of aortic runoff including patent ductus arteriosus, ruptured sinus of Valsalva, coronary arteriovenous fistula, and aortic–left ventricular tunnel.

Once the diagnosis of aortic valve disease has been established, it is important to establish the etiology. A history of rheumatic fever and/or evidence of organic mitral valve disease favors rheumatic etiology. If there is evidence of associated significant aortic stenosis (supravalvular, valvular, or discrete subvalvular), the cause of aortic insufficiency is usually congenital. Isolated congenital aortic insufficiency is very rare and can occur with aneurysms of the sinus of Valvalva. Other causes of aortic insufficiency at a young age include aortic insufficiency that occurs with coarctation of the aorta, ventricular septal defect, and Marfan's syndrome.

An important differential diagnosis is infective endocarditis on a congenitally deformed aortic valve. This will lead to combined aortic stenosis and insufficiency. Differentiation between infective endocarditis and rheumatic fever is described in the Chapter 86 on rheumatic fever.

RHEUMATIC TRICUSPID VALVE DISEASE

Rheumatic tricuspid valve disease is almost invariably associated with mitral or aortic valve disease. While very few cases of isolated rheumatic tricuspid stenosis have been reported,[86] isolated incompetence has not been described.[87]

The incidence of tricuspid valve disease differs according to the criteria involved, whether clinical and hemodynamic or pathologic and surgical. Microscopic evidence of rheumatic inflammation of the tricuspid valve has been found as often as in the mitral valve, but significant clinical regurgitation or stenosis is far less common. The incidence of clinical tricuspid disease now is greater than was recognized previously; there is now increased awareness, more precise diagnosis, and, most important, routine exploration of the tricuspid valve at the time of operation for mitral valve disease. Tricuspid valve disease was noticed in about 30% of patients operated on for mitral valve disease in areas where rheumatic heart disease is prevalent; half of these cases required correction.[88,89]

Pathology

Organic Tricuspid Stenosis

Tricuspid stenosis is present on pathologic examination in 5 to 10% of patients with rheumatic heart disease and is always associated with more severe mitral valve disease.[90,91] It is a consequence of rheumatic valvulitis, which causes inflammation and scarring, leading to commissure fusion with narrowing of the orifice area. Leaflet and chordal thickening sometimes occur but with much less extent.

Organic Tricuspid Incompetence

Organic tricuspid incompetence can occur either alone or with organic tricuspid stenosis as a result of rigidity of orifice edges, shrinkage of leaflet tissue, annular dilatation, or a combination of these abnormalities.

Functional Tricuspid Incompetence

Functional tricuspid incompetence occurs because of annular dilation and malalignment of papillary muscles due to right ventricular failure complicating pulmonary hypertension or loss of contraction of the tricuspid annulus during atrial fibrillation.[90] Anatomic studies proved that annular dilatation is asymmetrical, affecting the posterior and anterior leaflets and commissured areas and sparing the septal side of the annulus.[92] Partial tilting of the ring was proposed as a mechanism of functional tricuspid incompetence leading to a gap between the septal leaflet and the anterior and posterior leaflets.[89]

Pathophysiology

Tricuspid incompetence permits blood to regurgitate into the right atrium, leading to initial diminution of the forward flow by the same amount. The larger volume of blood in the right atrium increases the pressure of the v wave so that when the right ventricle relaxes, it becomes subjected to higher filling pressure and dilates more to accommodate this extra blood. In this sense, augmented diastolic filling will compensate for the leak. Right ventricular dilation will intensify the leak and magnify the heart failure. So tricuspid incompetence may both augment and be augmented by congestive heart failure. Myocardial resistance and a restraining effect of the pericardium act in the opposite direction to stop this vicious circle.

As regards tricuspid stenosis, its cardinal feature is a diastolic pressure gradient across the tricuspid valve with elevation of right atrial pressure. This gradient varies with heart rate, cardiac output, exercise, and respiration. It is marked in presystole in sinus rhythm, and in early diastole in atrial fibrillation.[93] If tricuspid stenosis is suspected, the gradient must be measured between the right atrium and right ventricle simultaneously.[94]

Symptoms

Symptoms of pulmonary congestion are less common and less severe in patients with predominant tricuspid stenosis than in those with predominant incompetence. This is because of the reduced right ventricular filling secondary to obstruction of blood flow.

However, symptoms are dominated by the associated more severe left-sided lesions.

General Examination

General signs are caused by elevated systemic venous pressure due to either tricuspid valve obstruction or incompetence. With tricuspid incompetence, there is a prominent systolic CV wave in the jugular venous pulse and rapid Y descent. With tricuspid stenosis, there is a brief, sharp, tall a wave; there is a flickering a wave in patients with sinus rhythm. In both conditions, the liver is enlarged and tender. There may be edema, ascites, and sometimes protein-losing enteropathy. Systolic pulsation may be noticed in most patients with significant tricuspid incompetence. Liver congestion commonly leads to impaired liver function with elevated serum bilirubin and mild icterus, giving the patient a characteristic appearance. There may be cold hands with peripheral cyanosis because of low cardiac output.

Auscultation

The murmur of tricuspid incompetence is audible at the lower left sternal border, is pansystolic and usually followed by a third sound, and may radiate to the apex. Inspiration may increase the intensity of the murmur and may also change its character. This murmur is inconstant and may vary from day to day in its intensity.[95]

The diastolic murmur of tricuspid stenosis mimics that of mitral stenosis. However, it is usually best heard at the lower left sternal border and has a higher pitch than that of mitral stenosis. A tricuspid opening snap may be audible.

Generally, tricuspid murmurs tend to increase with inspiration, but this is usually difficult to elicit in many patients because of gross heart failure. Also, lung expansion during inspiration interferes with auscultation.

The clinical diagnosis of tricuspid stenosis may be difficult. The available signs—flickering a wave (rapid rise and slow descent), inspiratory increase of diastolic murmur, and right atrial enlargement—all give presumptive evidence of tricuspid valve disease. Despite the greater ease in diagnosing tricuspid incompetence, there is no pathognomonic sign.

Electrocardiography

Electrocardiogram changes with tricuspid incompetence are nonspecific. There may be evidence of right atrial enlargement and right ventricular hypertrophy. Atrial fibrillation is present in most of these patients. Tricuspid stenosis is suggested in the presence of a tall, peaked P wave with a long PR interval without right ventricular preponderance.

Roentgenography

In tricuspid stenosis, right atrial enlargement may be out of proportion to pulmonary hypertension. No correlation has been found between the right atrial enlargement and C/T ratio and the severity of tricuspid valve disease.

Echocardiography

M-Mode Echocardiography

The normal tricuspid valve M-mode echocardiogram has a pattern of motion similar to that of the mitral valve. However, in normal subjects, it is usually difficult to record the entire motion of the tricuspid valve. The tricuspid valve is recorded easily only if there is right ventricular enlargement.[96]

The criteria used to diagnose tricuspid stenosis on an M-mode echocardiogram include a diminished EF slope, anterior displacement of the posterior tricuspid leaflet, and thickening of the valve.[97] However, there are problems with each of these criteria. In rheumatic heart disease, there is often concomitant pulmonary hypertension and right ventricular hypertrophy secondary to mitral valve disease. This may diminish the tricuspid EF slope,[98] but if the reduced EF slope is associated with a reduced DE amplitude of excursion (less than or equal to 10 mm), the diagnosis of tricuspid stenosis is more likely.[99] The anterior displacement of the posterior leaflet of the tricuspid valve cannot always be detected; therefore, when it is absent, tricuspid stenosis cannot be excluded.[98] Thickening of the cusps indicates a diseased valve that is not necessarily stenotic.[99]

Two-Dimensional Echocardiography

There is no specific picture for diagnosis of tricuspid insufficiency by two-dimensional echocardiography. "Tricuspid leaflet thickening, doming of the valve, and restricted leaflet motion" were found in each of four cases with hemodynamic evidence of tricuspid stenosis in a series of 100 patients with rheumatic heart disease.[98] Similar findings were not present in any of the remaining 96 patients who did not have tricuspid valve gradients. The reported sensitivity and specificity for the two-dimensional echocardiogram study in the diagnosis of tricuspid stenosis were both 100%. Another study[100] reported a sensitivity and a specificity of 69% and 96%, respectively, in a group of 38 patients who had both echocardiographic and hemodynamic evaluation.

Contrast Echocardiography

Contrast echocardiography done by rapid injection of saline into the antecubital vein is a very sensitive tool for detecting tricuspid incompetence.[101] However, it yields false-positive results in 10% of cases with a predictive value of 90% and is considered a good negative test to exclude tricuspid incompetence.[89] In terms of positive results, microcavitation can be seen moving back and forth across the tricuspid valve and can be seen in the inferior vena cava and hepatic vein during systole.

Doppler Echocardiography

Doppler echocardiography is the most reliable noninvasive method for assessing the severity of tricuspid regurgitation, and it is useful even in patients with atrial fibrillation, congestive heart failure, or right ventricular pressure overload.[102] Doppler echocardiography has shown the low sensitivity of clinical diagnosis of tricuspid regurgitation.

In 1982, Miyatake and colleagues[103] reported pansystolic abnormal Doppler signals in the right atrial cavity in 58 of 62 patients with suspected tricuspid regurgitation. The tricuspid regurgitation was graded on a scale of 1 to 4+ on the basis of the distance traveled by the abnormal signals from the tricuspid orifice toward the posterior right atrial wall. The right ventriculograms were also graded on a four-point scale. Grades matched exactly in 36 patients but differed by one point in 23 patients and by two points in 3 patients.

A noninvasive estimate of right ventricular systolic pressure can

be obtained by Doppler by calculating the pressure gradient between the right ventricle and the right atrium in systole from the maximal velocity jet in tricuspid regurgitation.[25]

The presence of tricuspid stenosis is easy to diagnose with Doppler ultrasound, and the pressure drop calculated from the maximal velocity seems so far to correlate well with the pressure drop obtained by catheter withdrawal from the right ventricle to the right atrium.[25,104]

Hemodynamics and Angiographic Studies

In tricuspid insufficiency, the right atrial and right ventricular end-diastolic pressures are elevated. The right atrial pressure shows an absence of X descent and a prominent CV wave. In severe cases, there is ventricularization of right atrial pressure. Right ventricular angiography is not a good method to diagnose and assess the degree of tricuspid incompetence, since the catheter across the tricuspid valve may induce incompetence, leading to a false-positive result. However, there are some claims that this method can be used to evaluate tricuspid incompetence.[105]

Cardiac catheterization provides the most reliable means of quantifying the degree of tricuspid stenosis. A small diastolic gradient of 2 mm Hg across the tricuspid valve is sufficient to establish diagnosis, and a gradient of 5 mm Hg implies significant stenosis sufficient to produce systemic venous congestion. This gradient is presystolic in sinus rhythm and early diastolic in atrial fibrillation. If tricuspid stenosis is suspected, right atrial and ventricular diastolic pressure should be recorded simultaneously. However, rarely, significant tricuspid stenosis may not be associated with a diastolic gradient.[106] Right atrial angiography in a 30% right anterior oblique position demonstrates a characteristic doming of a tricuspid valve and delayed emptying of the right atrium, ejecting blood across a funnel-shaped tricuspid valve (Fig. 87–22).

TREATMENT OF RHEUMATIC HEART DISEASE

Prophylaxis

Treatment includes prophylaxis against rheumatic fever and its recurrences and against the occurrence of infective endocarditis.

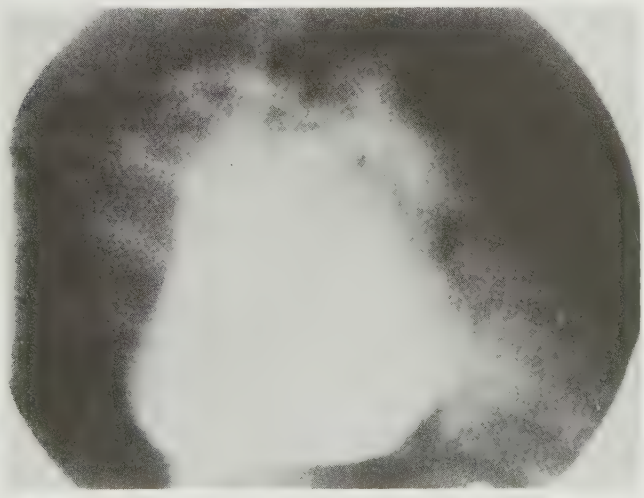

Fig. 87–22. Right atrial angiography in a patient with tricuspid stenosis showing markedly dilated right atrium with delayed emptying as well as funnel-shaped stenosed tricuspid valve.

Since rheumatic fever is linked to an antecedent group A beta-hemolytic streptococcal infection, prophylaxis is directed against streptococcal infections. The preferred form of continuous prophylaxis is the monthly intramuscular injection of 1,200,000 units of benzathine penicillin. If the patient is allergic to penicillin, oral erythromycin twice daily should be used. Although the American Heart Association recommends that penicillin prophylaxis be continued for life,[107] most cardiologists tend to discontinue rheumatic fever prophylaxis by the time the patient has reached age 50 in Western countries and age 25 in Eastern countries unless there have been attacks of acute rheumatic fever within the previous five to ten years.

Antibacterial prophylaxis for prevention of infective endocarditis should be used for all dental procedures, including filling and cleaning of teeth[108] as well as dental extractions. Prophylaxis should also be used in the event of other exposures to bacteremia, including genitourinary and gastroenterological surgical procedures.

Physical Activity

In asymptomatic patients with mild-to-moderate valvular disease with normal heart size or insignificant cardiomegaly, normal school activity should be encouraged. Restriction of activity is unnecessary and may be harmful. In symptomatic patients, the allowed activity should be the one that does not produce symptoms of fatigue, dyspnea, or excessive palpitation. Weight lifting and other isometric exercises should be discouraged. Competitive sports are not generally recommended, since the patient may tend to ignore symptoms in the excitement of a contest.

Management and Complications

Anemia and Infections

Patients with chronic rheumatic heart disease generally have diminished cardiac reserve. Cardiac decompensation can be precipitated by anemia and/or minor infections; therefore such factors should be treated both promptly and aggressively. Chest infections are often precipitated by fluid retention, so a diuretic is usually needed.

Arrhythmias

In rheumatic mitral valve disease, frequent premature atrial contractions often presage atrial fibrillation, and the administration of antiarrhythmic drugs may be effective in preventing this complication. Atrial fibrillation, flutter, and tachycardia can complicate such cases. The immediate treatment should be directed toward reducing the ventricular rate and, if possible, toward reestablishing sinus rhythm by pharmacologic treatment and cardioversion singly or in combination. Following reversion to sinus rhythm, administration of quinidine or a similar antiarrhythmic agent should be continued indefinitely to diminish the likelihood of recurrence.

Patients with significant mitral valve disease, hugely dilated left atria, and chronic atrial fibrillation (for six months or longer) who cannot be converted or maintained in sinus rhythm (including a trial of amiodarone) should receive adequate doses of digitalis to keep the ventricular rate at rest at approximately 60 to 65 beats per minute. If this is not feasible, small doses of a beta blocker or the slow channel calcium blocker verapamil may be added if the ventricular function is normal.

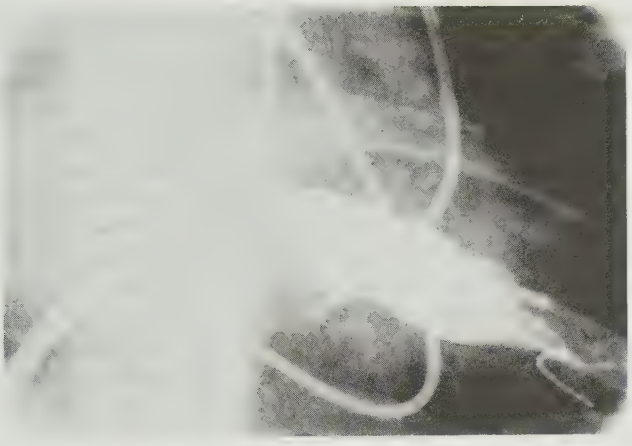

Fig. 87–23. Roentgenogram showing two inflated balloons across the mitral valve. Both were passed along wires after transseptal catheters.

Thromboembolism

As a general rule, anticoagulant therapy should be given to reduce the risk of embolism to all patients with atrial fibrillation unless there are very strong contraindications.

If an operation is not to be carried out, oral anticoagulants should be administered to patients with mitral valve disease who have suffered systemic emboli as well as patients who are at high risk of embolization, that is, those who are in atrial fibrillation, have greatly enlarged left atrium, and/or have a left atrial thrombus demonstrated by two-dimensional echocardiography.

Infective Endocarditis

Infective endocarditis is treated in the usual way.

Heart Failure

It is desirable to administer digitalis to patients with significant valvular lesions who begin to develop effort fatigue or dyspnea, with or without frank evidence of left or right heart failure. However, if a patient with isolated mitral stenosis does not have either right heart failure or atrial fibrillation or flutter, little hemodynamic benefit can be expected from the use of digitalis.[109] Fluid retention in such conditions responds well to treatment with diuretics. In addition, a low-sodium diet is advisable, especially if the diuretics are not completely effective. It should be emphasized that the measures designed to reduce pulmonary venous pressure, including sedation, assumption of upright posture, and aggressive diuresis are also used to treat hemoptysis of lung congestion.

Patients with frank cardiac failure are treated in the usual way. Uncontrollable heart failure in children must raise the possibility of severe valvular afflictions, rheumatic activity, infective endocarditis, or electrolyte imbalance.

The response to vasodilator therapy is impressive in cases of mitral and aortic insufficiency. Hemodynamic studies have shown beneficial effects of intravenous hydralazine[110] and oral prazosin.[111] This therapy may be helpful in stabilizing patients who are waiting for surgery. Moreover, agents such as nitroglycerine given sublingually may be effective in relieving dyspnea brought on by exercise and permit the same exercise to be taken with a lower pulmonary artery pressure by causing venous dilatation, arteriolar dilatation, or both.

Catheter Balloon Valvuloplasty

Dilatation of stenosed mitral valves by balloon valvuloplasty catheters is emerging as a successful way of relieving mitral obstruction[112,113] (Fig. 87–23). This procedure is currently used in patients with sinus rhythm who have pliable mitral noncalcified leaflets and do not have left atrial thrombi. Dilatation of tricuspid stenosis has also proved very helpful in some patients[114] (Fig. 87–24). This technique would be ideal in children, who have pliable noncalcified leaflets, to avoid thoracotomy.

Surgical Treatment

Although the only direct therapy of cardiac valve disease is surgical, management of children with this illness should conserve the natural valve whenever possible. There is no prosthesis that is totally free of thromboembolic and anticoagulation problems and that has an effective orifice that will not be outgrown by a small child.

Currently, available tissue heterografts are prone to calcification and early tissue failure in the aortic and mitral positions and cannot be recommended in children except under unusual circumstances. Tissue valves continue to be the valves of choice for the tricuspid and pulmonary positions.

On the basis of our current knowledge, it is recommended that mechanical aortic and mitral valves be used for children (Fig.

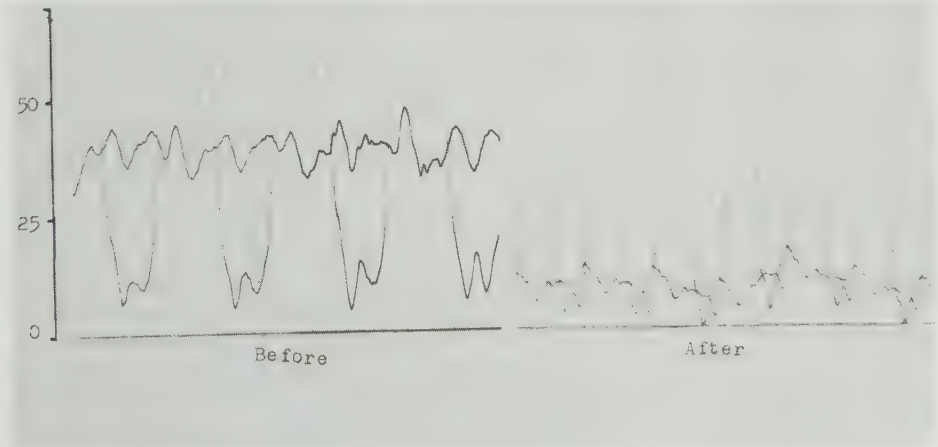

Fig. 87–24. Tracing on left demonstrating 30 mm Hg diastolic gradient from LA–LV; in tracing on right, after balloon mitral valvuloplasty gradient is essentially eliminated. Shows a drop in the left atrium–left ventricle diastolic gradient by balloon mitral valvuloplasty.

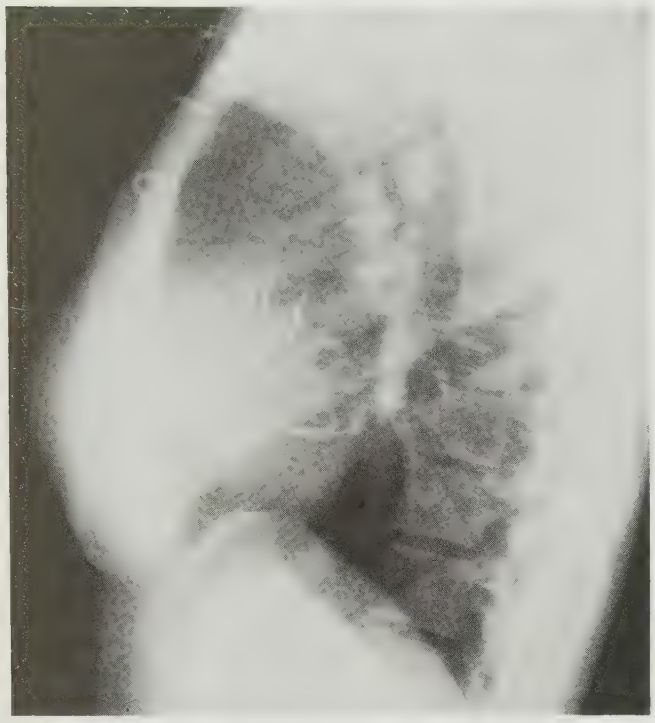

Fig. 87–25. Lateral chest radiograph showing the stents of mitral and aortic valves placed at a young age.

87–25). It is also recommended that anticoagulant therapy be used with all types of mechanical valve prostheses, even though the incidence of thromboemboli is much lower in children than in adults.

The durability of recently introduced mechanical valves seems superior to that of certain previously introduced ones, but many more years of followup will be required to substantiate this alleged superiority.[115] Also, the modification of tissue valve fixation using low pressure instead of high pressure and the addition of anticalcification agents to tissue valves may improve their durability.[115]

We now turn to the particular problems associated with valve replacement in the pediatric age group.

Surgical Treatment of Mitral Stenosis

Mitral stenosis causes mechanical obstruction to the circulation, and the most satisfactory treatment is opening the obstruction. A number of procedures are available, including open or closed mitral valvotomy, mitral valve replacement, and balloon dilation. The choice depends on the anatomy of the mitral valve determined by assessment of the physical signs, echocardiogram, age of the patient, and resources available.

The decision about the first operation is an important one, since it represents the initial stage in the lifetime care of the patient's mitral valve. Closed mitral valvotomy is a relatively simple procedure in terms of the resources that are required, although a satisfactory result presupposes considerable surgical expertise. It is particularly suitable in a young patient in sinus rhythm with evidence of a mobile anterior cusp.

Open valvotomy requires cardiopulmonary bypass but allows a more complete procedure to be undertaken and, in particular, allows the subvalvular apparatus to be inspected and adherent chordae to be divided. If the results of valvotomy are found to be unsatisfactory, then it is possible to proceed to valve replacement in the same operation. If the valve cusps are greatly thickened or calcified, then mitral valve replacement is required. This operation should not be considered for patients in whom the hemodynamic disturbance caused by the valve disease is mild, since resting diastolic pressure gradients and abnormal left ventricular filling can be demonstrated with all currently available mitral prostheses.

In summary, if the clinical evidence suggests that a valvotomy is feasible, then the presence of definite limitation of exercise tolerance is an adequate indication, particularly in a young person. If valve replacement is likely to be required, the decision to operate requires more severe symptoms.

Timing of Surgery in Chronic Mitral and Aortic Insufficiency

Chronic mitral and aortic insufficiency share the same physiologic and clinical features. Both valvular lesions impose a volume load on the left ventricle, leading to chamber dilatation and myocardial hypertrophy. The natural history of both lesions is characterized by a long asymptomatic period; and when congestive heart failure develops, valve replacement is effective in alleviating symptoms. At the same time, myocardial dysfunction initially occurs at a subclinical level in both conditions and may become irreversible before symptoms of congestive heart failure develop.[116]

The timing of surgery for these two conditions is controversial. Because it is difficult to predict the onset of left ventricular dysfunction, arguments have been made in support of early surgery even in the absence of symptoms.[117,118] The arguments for early intervention have been disputed on the basis of operative mortality and prosthesis complications[119] as well as the relatively benign natural history of patients who remain asymptomatic.[120] At the same time, delay in performing surgery when left ventricular dysfunction is severe is associated with higher operative mortality and poor postoperative course.

Surgery for chronic rheumatic mitral or aortic insufficiency is clearly indicated in patients who have significant functional limitations, since valve replacement usually improves symptoms. However, functional class IV is associated with high operative mortality and poor long-term survival after valve replacement.

Because surgery is unwarranted in asymptomatic patients with normal ventricular function and may be of marginal benefit in severely symptomatic (functional class IV) patients, the question arises as to the time for surgery. The suggested approach for mitral insufficiency and for aortic insufficiency depends on multiple clinical, echocardiographic, and hemodynamic predictions of left ventricular function.

1. All patients with functional class III or IV congestive heart failure should have mitral valve replacement or aortic valve replacement.
2. All asymptomatic or mildly symptomatic patients should be evaluated for possible surgery. If the valve lesion is severe and there is evidence of left ventricular dysfunction, surgery must be considered. If the left ventricular function is normal, it may be appropriate to follow the patients. Any evidence of left ventricular dysfunction is an indication for surgery.

Surgery of Rheumatic Tricuspid Valve Disease

There is still controversy as to whether the decision to correct a tricuspid valve lesion can be made preoperatively. Some believe that the assessment can be made accurately by hemodynamic and angiographic studies.[121–123] Others believe that finger exploration before cardiopulmonary bypass is mandatory to assess the valve function in patients subjected to mitral or aortic valve surgery.

Until recently, management of tricuspid incompetence has also been controversial. Some have advocated conservative management, others have advised replacement,[124] and some have recommended repair.[125] It has been found that the presence of tricuspid valve disease seriously compromised the results of operations for mitral valve disease.[122] Tricuspid valve replacement is rarely performed because no valve has proven ideal.[126] The majority of cases with tricuspid incompetence can be corrected by valve reconstruction. Even mild tricuspid incompetence should be corrected during initial operation for associated valve lesions because of the unpredictability of the course in these patients.

DeVaga semicircular suture annuloplasty and Carpentier flexible ring have offered excellent solutions for the problem of tricuspid incompetence.[127,128]

As regards tricuspid stenosis, open tricuspid commissurotomy has become the procedure of choice, since it offers complete and safe correction of the stenosed valve.[129]

Problems Associated with Valve Replacement

In areas where rheumatic fever is prevalent and severe, valvular damage may necessitate early surgery in increasing numbers of patients. Valve replacement in this age group is plagued by a myriad of problems in the preoperative, intraoperative, and postoperative phases (Table 87–1).

Preoperative Problems

Rheumatic activity can be lingering and sometimes almost continuous.[130] Children with chronic rheumatic activity and severe valvular damage may have to undergo surgery without waiting for quiescence of activity. The impact of this on long-term survival has not been studied.

Table 87–1. Problems Associated with Valve Replacement in the Pediatric Age Group

Problems in the preoperative period:
Persistent rheumatic activity
Lack of compliance with treatment
Choice of prosthesis
Intraoperative problems:
Small annulus
Small ventricular cavity
Damage to conduction system
Postoperative problems:
Difficulties with anticoagulation
Recurrence of rheumatic activity
Prosthesis malfunction caused by small ventricular cavity
Ventricular dysfunction caused by large prosthesis size
Problems with reoperation:
Higher morbidity and mortality of redo surgery in general
Small annulus
Coronary ostial stenosis (?)

Most youngsters comply poorly with long-term medication, diet, and effort restriction and may thus have to undergo surgery in a less than optimal condition.

The choice of prothesis in this age group is a real dilemma.[131–133] Caged ball valves are too bulky for small cardiac chambers, and the hydrodynamic characteristics of small sizes are poor. Tilting disc valves, on the other hand, are less bulky, but their excursions are often limited by small chamber size, leading to stenosis, incompetence, and increased thrombogenicity because of stasis.[134] Bioprosthetic valves have high failure rates, particularly in young patients. Failures may be the result of dissolution of collagen, thrombosis, calcification, or a subtle form of graft rejection.[135–137] Promising results have recently been obtained with developments in artificial valve technology. The most prominent of these is the development of third-generation (supra-annular) Carpentier-Edwards valves,[138] the monostrut Bjork-Shiley valve,[139] the Medtronic-Hall valve,[140] and the St. Jude valve. These prostheses have a low gradient even with small sizes and are thus of potential benefit in pediatric valve replacement.

Intraoperative Problems

The implantation of a relatively large valve may be difficult because of a small annulus, more commonly so in the aortic position. Several procedures have been tried to enlarge the left ventricular outflow tract. The most commonly used is the Konno procedure, in which the aortic annulus is divided, the ventricular septum is incised, and the anterior mitral leaflet is incised to provide space for valve implantation.[141,142] This procedure may damage the conduction system, create mitral incompetence, and render further reoperation technically difficult.

As was mentioned earlier, the left ventricular outflow tract may be too small for the implantation of a caged ball prosthesis in the mitral position.

Postoperative Problems

Compliance of young patients with long-term anticoagulant therapy is poor.[143] On the other hand, the more vigorous life they lead makes them more liable to trauma and serious hemorrhage when on anticoagulant therapy. The use of platelet aggregation inhibitors[144,145] and pentoxifylline[146] is currently under trial.

Recurrence of rheumatic activity can still be encountered after valve replacement in this age group. The subsequent further valvular and/or myocardial damage can alter the prognosis and make further surgery more risky or less useful.

Prosthesis malfunction caused by a small ventricular cavity may lead to limited excursions with subsequent prosthesis stenosis, incompetence, and stasis, leading to increased thrombogenicity.

Of equal importance is poor ventricular performance caused by a large prosthesis in the ventricular cavity. Ventricular dysfunction is probably caused by (1) mechanical interference with ventricular emptying, (2) loss of papillary muscles, and (3) lack of the normal contraction of the mitral (or tricuspid) annulus during ventricular evacuation, that is, loss of annulus function.[147]

There are no data to indicate whether young patients with artificial heart valves are more prone to infective endocarditis than older patients. The same applies to prosthesis-induced hemolysis.

Problems with Reoperation

Valves implanted before the rapid growth phase of adolescence will invariably need to be replaced during adulthood because of

disparity of valve size and the need for increased cardiac output. Apart from the increased mortality and morbidity of redo surgery in general, the aortic and/or mitral annulus may, at the time of reoperation, be too small for the now-appropriate prosthesis size. Annulus enlarging procedures (e.g., Konno) or left ventricular apicoaortic conduits[148] may be required.

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CHAPTER 88

Cardiovascular Manifestations of Connective Tissue Diseases

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Connective tissue disease is a term used to describe any one of many disorders of uncertain cause, which have overlapping clinical manifestations and may share common mechanisms of pathogenesis. This chapter deals with the more common connective-tissue diseases of childhood, including juvenile rheumatoid arthritis, systemic lupus erythematosus, drug-induced lupus, neonatal lupus, the spondyloarthropathies (including juvenile ankylosing spondylitis, Reiter's syndrome, and arthritis associated with inflammatory bowel disease), and Lyme disease. The most apparent clinical symptoms involve the joints and skin; however, each of the diseases may have a systemic component that affects the cardiovascular system. The spectrum of cardiac involvement includes pericarditis, myocarditis, endocarditis, coronary artery disease, systemic arteritis, pulmonary hypertension, and conduction system abnormalities.

JUVENILE RHEUMATOID ARTHRITIS

Juvenile rheumatoid arthritis (JRA) is the most common pediatric connective-tissue disease. The following classification enumerates the requirements for a diagnosis of JRA and the three clinical onset subtypes.[1] By definition, JRA begins before the age of 16 years. Persistent arthritis of one or more joints of at least 6 weeks' duration is sufficient for diagnosis if other causes of arthritis are excluded. Arthritis is defined as swelling of a joint or limitation of joint motion, with heat, pain, or tenderness. Pain or tenderness alone is not sufficient for the diagnosis of arthritis.

The onset subtype is determined by manifestations that occur during the first 6 months of disease. Systemic-onset JRA is defined as JRA with persistent intermittent fever (daily intermittent temperatures of 103°F or more) with or without rheumatoid rash or other organ involvement. Typical fever and rash are considered *probable* systemic-onset JRA if they are not associated with arthritis; however, before a definite diagnosis can be made, arthritis, as defined above, must be present. Children with systemic-onset JRA make up 10 to 30% of the cases of JRA. The sex ratio is equal or with a slight male preponderance. In addition to the fever and rash, extra-articular findings may include hepatomegaly, splenomegaly, generalized lymphadenopathy, pericarditis, pleuritis, and nonspecific abdominal pain. The laboratory findings in the classic picture include anemia, leukocytosis, and an elevated sedimentation rate. Antinuclear antibodies, rheumatoid factor, and HLA-B27 are usually negative. Approximately 40% of these patients will develop evidence of severe, progressive joint disease.[2]

Pauciarticular-onset JRA is defined as JRA with arthritis involving four or fewer joints; it accounts for 40 to 50% of JRA cases. Patients with systemic-onset JRA are excluded from this onset group. Within this group there are three different subtypes. Subtype I occurs predominantly in girls (female:male ratio, 6:1); onset is typically in early childhood, and at some point iritis develops.[2] Antinuclear antibodies are usually positive in this subgroup.[3] The iridocyclitis occasionally precedes joint complaints, but more often occurs at the onset of joint symptoms or during the course of the disease. The iridocyclitis is often chronic and insidious with great potential for ocular damage. Subtype II typically occurs in older boys (male:female ratio, 9:1) with lower extremity arthritis. Rheumatoid factor and antinuclear antibodies are often negative. More than half these patients are positive for HLA-B27.[4,5] These children often later develop sacroiliitis. In the

second or third decade of life, when sacroiliac or lumbar arthritis becomes apparent, patients with this subtype may fulfill the criteria for ankylosing spondylitis or another of the spondyloarthropathies. Subtype III of pauciarticular-onset JRA involves children with arthritis in four or fewer joints who do not develop either iritis or sacroiliitis.

Polyarticular-onset JRA is characterized by the presence of arthritis in five or more joints, and occurs in approximately 40 to 45% of children with JRA. There is a female preponderance. The majority of children with polyarthritis have negative results for rheumatoid factor. A subgroup of patients will have positive rheumatoid factors. Those with positive rheumatoid factors are more likely to develop severe chronic arthritis and therefore have a worse prognosis than those who are rheumatoid factor–negative. The subgroup with positive rheumatoid factors closely resembles classic adult-onset rheumatoid arthritis.

Cardiovascular Manifestations of JRA

Pericarditis

The principal cardiac findings in children with JRA relate to pericarditis, ranging from completely asymptomatic patients with echocardiographic findings of minimal pericardial effusions to patients with severe life-threatening cardiac tamponade. Before the availability of the echocardiogram, pericarditis was recognized clinically in approximately 10% of children with JRA.[6] Autopsy reports, however, have revealed an incidence of pericarditis as high as 45%.[7] In a study by Lietman and Bywaters, the pericarditis was unrecognized clinically in the majority of patients.[7] With the advent of echocardiography, more accurate assessment of the incidence of pericarditis in JRA is available. Bernstein et al.[8] obtained echocardiograms, ECG, and chest radiographs from 55 patients with JRA. Twenty (36%) had echocardiographic evidence of pericarditis. Of these patients, ECGs were normal in 12 and abnormal in eight. Cardiac size by chest radiograph was normal in 11, with cardiac enlargement in nine. In at least 11 of the 20 patients with a positive echocardiogram, the diagnosis of pericarditis was not otherwise apparent. Other studies have revealed a lower incidence of pericarditis. Brewer[9] obtained echocardiograms from 50 consecutive patients with JRA. Of these 50, 45 were normal and had no clinical symptoms of pericarditis, three were clinically ill with pericarditis and had echocardiographic evidence of pericardial effusions, and two patients had minimal pericardial effusions without clinical findings suggestive of pericarditis.

The occurrence of pericarditis may occasionally precede the onset of arthritis, but this is unusual. Some patients have pericarditis at the time of disease onset, but the majority develop clinically apparent pericarditis several months or even years after the onset of arthritis.[2,7] Pericarditis occurs more often in patients with systemic-onset disease than in patients with polyarticular- or pauciarticular-onset disease,[7–9] and frequently accompanies a flare of systemic symptoms, especially fever. Patients with pericarditis are more likely to have a rash, lymphadenopathy, splenomegaly, pulmonary disease, or amyloidosis than patients without pericarditis.[7] They are also more likely to have lower hemoglobin levels, higher white blood cell counts, and higher sedimentation rates than patients without pericarditis.[8]

Clinical Presentation of Pericarditis. Brewer et al.[2] have divided the clinical presentation of pericarditis into the following groups.

Subclinical Pericarditis. The advent of echocardiography has made apparent that there is a group of patients with echocardiographic evidence of pericardial effusions who have a normal physical exam, chest radiograph, and ECG.[8,9] Precordial pain and dyspnea are frequently absent in the JRA patient with pericarditis; most attacks of pericarditis remain asymptomatic and undetected.[10] Consequently, clinicians should suspect pericarditis in all patients with prominent systemic manifestations. The child should be examined regularly for the appearance of a friction rub, pulsus paradoxus, or cardiomegaly, and screened intermittently for abnormalities on ECG and echocardiogram. In most cases, the pericarditis will resolve spontaneously.

Mild Pericarditis. Mild pericarditis is characterized by an intermittent or constant friction rub with mild cardiac enlargement on chest radiograph.[2] Patients with this condition may demonstrate tachycardia and nonspecific ECG changes. These patients are usually minimally symptomatic, but occasionally will complain of mild shortness of breath or minimal chest pain with exertion. The episode often subsides spontaneously.

Moderately Severe Pericarditis. Patients with moderately severe pericarditis often complain of chest pain aggravated on assumption of the supine position and worsened with deep inspiration. Pericardial friction rubs, tachycardia, and tachypnea or dyspnea are common. A typical episode may last for weeks or months with periodic exacerbations and partial remissions.

Severe Pericarditis with Cardiac Tamponade. Cardiac tamponade secondary to severe pericarditis is an extremely uncommon complication of JRA. In their series of 55 patients with JRA and cardiac involvement, Bernstein et al.[8] had no patients with tamponade. Schaller and Wedgewood[11] reported only two cases of severe pericarditis in a review of 124 JRA patients, and no patient had tamponade. The literature contains only a few documented cases of cardiac tamponade related to JRA.[6,12–14] In these reports, the tamponade occurred only in children experiencing significant systemic flare-up of their JRA, and was accompanied by high fever, hepatomegaly, and arthritis. In one series,[6] two of three patients had been treated with phenytoin prior to the onset of cardiac involvement and the authors speculated that this medication may predispose children with systemic JRA to develop severe pericarditis and tamponade. In some of the patients cited in the literature, pericardiocentesis revealed a serosanguineous fluid with a neutrophilic pleocytosis, diminished concentrations of glucose and hemolytic complement, high levels of acid phosphatase and lactic dehydrogenase, and the absence of rheumatoid factor.[12,13] Obtaining these laboratory parameters may help in distinguishing the pericarditis of JRA from infectious pericarditis occurring in a JRA patient. Constrictive pericarditis has not been reported as a longterm complication of severe pericarditis in JRA patients.

Treatment of Pericarditis. Treatment of pericarditis in JRA varies depending upon the severity of clinical involvement. Asymptomatic or mild pericarditis requires no additional therapy. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be adequate in the treatment of moderately severe pericarditis; however, some patients may require short courses of corticosteroid therapy. Treatment of severe pericarditis is generally the same as that for severe systemic JRA. Prednisone (1–2 mg/kg/day), or an equivalent drug, or high-dose pulse steroid therapy may decrease the associated

morbidity and also decrease the necessity of pericardiocentesis. Because of the rarity of tamponade, the best method of managing it is difficult to decide. Pericardiocentesis may be therapeutic in the presence of significant or progressive compromise of cardiac function. Diagnostic pericardiocentesis is occasionally required if an infectious pericarditis is suspected. One child was treated by pericardiocentesis and local corticosteroid injections,[12] while others have been treated with pericardiocentesis and systemic corticosteroids.[6,13]

Myocarditis

Myocarditis occurs much less frequently in the setting of JRA than does pericarditis, and few cases have been cited in the literature.[10,15–17] Bernstein et al.[8] have suggested that myocarditis may be present in as many as 10% of JRA patients. In that study, four of 40 JRA patients in whom systolic time intervals were studied had prolongation of the left ventricular pre-ejection period, suggesting decreased ventricular performance possibly indicating myocarditis.

Clinical Presentation of Myocarditis. Myocarditis usually occurs in a background of severe active systemic-onset JRA, and often recurs with flare-ups of systemic disease.[10,15,16] This situation is also the one in which pericarditis is most common, so that myocardial disease may be masked. Clues to impending myocarditis include the appearance of cardiomegaly and/or congestive heart failure (CHF) in the absence of substantial pericardial effusion; reduced ventricular function and/or cardiac dilation on echocardiogram; the appearance of sinus tachycardia inconsistent with the degree of fever or anemia present; tachypnea; changing heart sounds; arrhythmias; and the coexistence of pleuritis and/or pneumonitis.[10,15] The cause of the myocarditis in JRA is unknown. Its appearance with flare-ups of systemic disease suggests that the inflammation is due directly to disease activity, possibly to immune complex deposition in small vessels.[15] It is interesting that two of three patients in one series had syndromes similar to viral hepatitis prior to the attacks of myocarditis; however, no specific viruses were identified.[15] The possibility of viral myocarditis, therefore, needs to be considered. It is well known that viral illness may induce a flare-up of systemic disease in JRA patients. It is therefore possible that a viral illness may trigger the systemic features of JRA, including an inflammation of the myocardium. In another series of eight patients,[10] none had syndromes similar to viral hepatitis prior to the attacks of myocarditis, supporting the notion that myocarditis may be a feature of systemic inflammation secondary to the JRA itself.

Treatment of Myocarditis. The most effective treatment of myocarditis in JRA appears to be the use of high doses of corticosteroids. The avoidance of digoxin is recommended because the incidence of glycoside toxicity is high in these patients.[10,15] Clinical response to steroid therapy is usually dramatic, occurring within 24 to 48 hours. As steroids may be contraindicated in some forms of viral myocarditis, a careful clinical evaluation is necessary before starting treatment.[15] The signs of some viral infections that can cause myocarditis may mimic JRA, but differences in the rash, fever curve, joint disease, and systemic symptoms may help to distinguish these from JRA.

Valvular Involvement

Valvular heart disease is rare in patients with JRA. When present, valvular complications usually affect the aortic valve. Severe aortic insufficiency has been described in patients with all three onset types of JRA. Leak et al. described four patients with seropositive JRA and severe aortic incompetence.[18] Three of these four patients had subcutaneous nodules. Seropositive JRA resembles adult rheumatoid arthritis, and when valvular lesions occur in the adult patient, the aortic valve is the one most commonly affected. The valvular incompetence in this series of patients progressed in a short period of time. In cases with rapid progression to severe aortic regurgitation, aggressive surgical management may be necessary. The histology of the valves of two patients studied revealed destruction of the normal architecture by rheumatoid granulation tissue. In at least one case active nodular lesions were responsible for the destruction of the valve. Kramer et al. described severe aortic insufficiency in a patient with systemic onset JRA.[19] Histology of the valve of this patient revealed nonspecific changes with necrosis and fibrosis. Hull et al. described a patient with seronegative, HLA-B27–negative, pauciarticular-onset JRA with aortic incompetence, presumably due to aortitis.[20] Thus, both specific granulomatous nodules and nonspecific lesions have been found in the hearts of patients with JRA. Many of these patients eventually required valve replacement. Hull et al. reported clinical improvement with the use of chlorambucil, an immunosuppressive agent[20]; however, more cases need to be studied before one can safely assume a nonsurgical approach to the treatment of severe valvular disease. Criteria for aortic valve replacement in aortic regurgitation from rheumatoid arthritis are the same as those for congenital or rheumatic heart disease. Careful examination to identify even minor valvular abnormalities is important in the patient with JRA because of the need in these children for bacterial endocarditis prophylaxis.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a multisystem disease characterized by widespread inflammation and marked and varied immunologic abnormalities, including a variety of autoantibodies that participate in immunologically mediated tissue injury. Any organ system may be involved; multisystem involvement is common. In 1982, a revised set of criteria for the diagnosis and classification of SLE were established[21] (Table 88–1). The *malar rash* is described as a fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds. The *discoid rash* is described as erythematous raised patches with adherent keratotic scaling and follicular plugging. Atrophic scarring may occur in

Table 88–1. Revised Criteria for the Diagnosis and Classification of SLE*

Malar rash
Discoid rash
Photosensitivity
Oral or nasopharyngeal ulcerations
Arthritis
Serositis
Renal disorder
Neurologic disorder
Hematologic disorder
Immunologic disorder
Antinuclear antibody

*Four or more of the criteria should be present for a diagnosis of SLE.

older lesions. *Photosensitivity* may present as a skin rash as a result of an unusual reaction to sunlight. The *oral* or *nasopharyngeal ulcerations* are usually painless. The ulcerations are most common on the hard or soft palate. These ulcerations are usually not symptomatic and are likely to be noted only if looked for. The *arthritis* is characterized as nonerosive arthritis characterized by tenderness, swelling, or effusion. Joint involvement is a common manifestation of SLE and may precede the onset of multisystem disease by months to years. Deforming arthritis may occur but is unusual. *Serositis* includes pleuritis and pericarditis. Pleuritis is defined as a convincing history of pleuritic pain, a rub heard by a physician, or radiographic evidence of pleural effusion. Pericarditis is documented by ECG, by a friction rub, or by echocardiographic evidence of pericardial effusion. The clinical criteria for *renal involvement* include persistent proteinuria greater than 0.5 g per day (or greater than 3+ if quantitation is not performed) or the presence of cellular casts on urine microscopy, including red cell, hemoglobin, granular, tubular, or mixed types. The incidence of renal involvement has been cited to be as high as 60 to 80%.[22,23] The extent of renal involvement may vary from isolated histologic abnormalities on immunofluorescent studies, to mild proteinuria or hematuria, to nephrotic syndrome or frank nephritis.

Four main morphologic types of lupus nephritis have been identified.[24]

1. Mesangial (minimal) lupus nephritis, characterized by glomeruli that appear normal or merely show a slight irregular increase in mesangial cells and matrix. Immunofluorescent staining demonstrates IgG and C3 in the mesangium.
2. Focal (mild) lupus nephritis, characterized by segmental proliferation of some glomerular tufts while others appear normal.
3. Diffuse (severe) proliferative lupus nephritis, characterized by abnormalities of more than 50% of the total area of the glomerular tufts. Although the proliferation is irregular, all glomeruli are involved and usually most of each glomerulus is abnormal.
4. Membranous lupus nephritis, histologically similar to idiopathic membranous glomerulonephritis.

Neurologic disorders include seizures (in the absence of offending drugs or known metabolic derangements) and psychosis (also in the absence of offending drugs or known metabolic derangements). *Hematologic disorders* include hemolytic anemia with reticulocytosis, leukopenia less than 4000/μL on two or more occasions, lymphopenia less than 1500/μL on two or more occasions, thrombocytopenia less than 100,000/μL in the absence of offending drugs. These abnormalities are thought to be mediated by autoantibodies directed against the particular cell type. To fulfill the criteria for an *immunologic disorder* one must demonstrate a positive LE cell preparation, antibodies directed against native DNA, antibodies directed against Sm nuclear antigen, or a false-positive serologic test for syphilis confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test. *Antinuclear antibodies* are the final criteria and should be considered only in the absence of drugs known to be associated with "drug-induced lupus syndrome."

Four or more of the criteria listed in Table 88–1 and described above should be present for the diagnosis of SLE. Other manifestations of the disease may include fatigue, fever, weight loss, alopecia, Raynaud's phenomenon, myositis, myalgia, rheumatoid nodules, tenosynovitis, thrombophlebitis, abdominal pain, pancreatitis, hepatosplenomegaly, lymphadenopathy, conjunctivitis and/or episcleritis, peripheral neuropathies, pneumonitis, and the cardiac manifestations (described below).[25] The systems most commonly involved in children are the joints, skin, kidneys, and pleuropericardial surfaces.[22,23]

Laboratory evaluation in SLE generally reflects the presence of autoantibodies and immune complex disease. Hematologic parameters may reflect the presence of anti–red blood cell, antiplatelet, anti–white blood cell, or antilymphocyte antibodies, as mentioned above. Antinuclear antibodies are directed against nuclear constituents and are the most characteristic autoantibodies of SLE.[26] Several patterns of immunofluorescence have been described. Antibodies to native or double-stranded DNA are fairly specific for SLE.[27] Evaluation of antibodies to extractable nuclear antigens (anti-ENA antibodies) may be useful and include anti-Sm and antiribonucleoprotein (anti-RNP) antibodies. Complement determinations often reflect the presence of ongoing immune complex disease with low C3, C4, and hemolytic complement results. The determination of circulating immune complexes (Raji cell assay or C_{1q} binding assay, for example) will usually reveal positive results. Urinalysis may reveal microscopic hematuria, proteinuria, or both. Coombs' antibodies may be present. Some patients with lupus have a circulating antibody (IgG, IgM, or both) that prolongs phospholipid-dependent coagulation tests by binding to portions of the phospholipid moiety of prothrombinase (a complex factor Xa, factor Va, phospholipid, and calcium).[28] This antiphospholipid antibody is termed the *lupus anticoagulant*. The hallmark of the lupus anticoagulant is prolongation of phospholipid-dependent coagulation tests (PT, APTT, and clotting time) without correction by admixture with normal plasma.[29] There is a strong correlation between the presence of the lupus anticoagulant and elevated titers of antibody to cardiolipin; the presence of either or both is associated with a high incidence of thrombosis.[30] Thus, the name lupus anticoagulant is really a misnomer as it has become clear that it is more frequently encountered in patients without lupus and it is not generally associated with abnormal bleeding except when hypoprothrombinemia, thrombocytopenia, or a qualitative platelet defect is present.

Cardiovascular Manifestations of SLE

Cardiovascular abnormalities have been reported in 50 to 80% patients with SLE.[31] The involvement may range from a nondiagnostic murmur and ECG changes to pericarditis, myocarditis, Libman-Sacks endocarditis, arrhythmias, coronary arteritis, and complications of systemic and pulmonary hypertension. With the increase in survival, seen since steroids were introduced in the late 1940s, and with advancement of diagnostic modalities, cardiovascular manifestations of SLE have become more apparent.

Pericarditis

Pericarditis is the most frequent cardiac manifestation of SLE, occurring in up to 30% of children with acute systemic disease.

Clinical Presentation of Pericarditis. Pericarditis may be clinically represented by recurrent painless effusions or by classical precordial pain exacerbated by certain physical positions or by deep breathing. A pericardial friction rub is sometimes heard, but does not necessarily correlate with the symptoms of pericarditis.[32] Evidence of pericarditis has been found at autopsy in over 62%

of lupus patients, but only 25% of these cases had clinically manifest pericarditis.[32] Although massive pericardial effusions may occur in SLE, pericardial tamponade is unusual, occurring in fewer than 1% of patients in a large series.[33] When present, it may be more frequent in drug-induced diseases[34,35] (see the section on drug-induced lupus). Constrictive pericarditis has been described in teenage patients with lupus.[36] Purulent pericarditis is rare and is usually seen in the context of a patient receiving corticosteroid therapy. When present, these cases are usually secondary to Staphylococcus aureus infection; however, tuberculosis has also been reported.[33]

The ECG may be helpful in confirming the presence of pericarditis, and usually reveals nonspecific ST-T wave changes.[37] The abnormalities may improve as the disease is treated. The echocardiogram is the most sensitive method of confirming the presence of pericardial fluid. Pericardial thickening may be more common than pericardial effusion in patients with SLE.[38,39] When pericardiocentesis is performed, the pericardial fluid is generally an exudate that may be clear to hemorrhagic, with normal glucose; numerous leukocytes; predominantly polymorphonuclear cells; and evidence of an immunologically mediated process with the presence of LE cells, antinuclear antibodies, anti-DNA antibodies, rheumatoid factor, immune complexes, and cryoglobulins.[32,33,40,41] The pericardial fluid complement in lupus patients is also lower than predicted values (pericardial fluid complement is usually one third that in serum); however, this is not specific for lupus.[41] Pathologically, the pericardium may be affected diffusely or focally.[33] In chronic cases the pericardial space may be obliterated by fibrous adhesions. In more acute cases, fibrous exudates may be found. The fact that pericardial involvement has frequently been detected in autopsy studies in patients who had neither signs nor symptoms of pericarditis may indicate that much of the pericardial involvement in SLE is asymptomatic and subclinical.[32,37]

Treatment of Pericarditis. The management of pericarditis in SLE depends upon the severity of involvement.[32,33,41] Asymptomatic, hemodynamically insignificant pericardial effusions do not generally require treatment. NSAIDs are often effective in symptomatic cases. More serious cases may require corticosteroid therapy. Steroids are usually effective in resolving the symptoms and diminishing the pericardial fluid within a few days, without the necessity of pericardiocentesis. Absence of any response to corticosteroids should warn of the possibility of infectious pericarditis even in a patient with an established diagnosis of lupus.[42] Pericardial tamponade may require pericardiocentesis; however, there is no clear cut role for intrapericardial steroid administration.

Myocarditis

Myocarditis involvement in SLE is much less common than is pericarditis.

Clinical Presentation of Myocarditis. Clinical manifestations of myocarditis include tachycardia, an enlarging heart, CHF, arrhythmias, and conduction defects. The clinical diagnosis of lupus myocarditis was made in 8% of 520 cases of lupus described by Dubois; the diagnosis was based on the presence of tachycardia out of proportion to fever, cardiomegaly, or a gallop rhythm.[43] Many of these patients had concomitant pericarditis. Bulkley and Roberts described myocardial inflammation in only eight of 36 autopsy patients.[44] Strauer et al. demonstrated that lupus cardiomyopathy may affect the intrinsic contractile properties of the myocardium and may exist even in young patients without clinical signs of cardiac dysfunction.[45] They studied five patients with SLE who had no clinical signs of cardiac dysfunction except for a soft and uncharacteristic systolic murmur. Electrocardiogram and chest radiographs demonstrated no arrhythmias, conduction defects, cardiac hypertrophy, or cardiomegaly. They found abnormalities of myocardial contractility and coronary hemodynamics in all five patients, including 1) increases in right and left ventricular end-diastolic pressures; 2) decreases of indices of cardiac contractility; 3) increases of end-systolic volume and decreases of the ejection fraction of the left ventricle; 4) increases of left ventricular wall stiffness as indicated by increases of dP/dV; and 5) normal coronary blood flow under resting conditions, although there was a marked reduction of coronary vascular reserve. Whether there is a cardiomyopathy directly attributable to lupus is uncertain. Other factors contributing to CHF in patients with SLE must be considered, including fever, infection, anemia, uremia, hypertension, steroid use, and accelerated atherosclerosis.[33] There is some evidence that immune dysfunction in lupus may contribute to the pathogenesis of the cardiomyopathy. Borenstein et al. reported that lupus myocarditis is frequently associated with generalized skeletal muscle myositis.[46] The patients in that study also demonstrated circulating antibodies to nuclear RNP in high titer. These findings suggest a possibility of a common pathogenetic mechanism for cardiac and skeletal muscle inflammation in SLE and lend support to a possible association of anti-RNP antibodies with inflammatory muscle disease in these patients. Das and Cassidy described anti-heart antibodies in 20 of 32 patients with SLE.[47] Antibodies were present with equal frequency in patients with and without clinical cardiac disease. The authors postulated that these antibodies represented an immunologic response to release into the circulation of altered myocardial antigen. Bidani et al. found evidence of immune complex deposition in nine of 10 necropsies and proposed that immune complex deposition may lead to complement activation, inflammation, and myocardial damage.[48] Either mechanism—anti-heart antibodies or immune complex deposition—may cause small vessel vasculitis, focal myocarditis, febrosis, and myocardial necrosis.[33]

Treatment of Myocarditis. Digitalis glycosides and diuretics are indicated when lupus patients develop cardiac insufficiency. If lupus myocarditis is suspected, corticosteroid therapy should be considered.[32]

Myocardial Infarction and Coronary Artery Disease

Acute myocardial infarction (MI) has been reported early in the course of disease in young SLE patients, including some patients who had not previously received steroids.[49–56] A number of causes have been proposed, including coronary arteritis,[32,33,44,54] thrombosis,[50,51] accelerated coronary artery atherosclerosis,[44,49,53,55] and coronary artery spasm.[52] The thrombosis, when present, is often associated with anticardiolipin antibodies and the lupus anticoagulant (discussed earlier). The accelerated coronary artery atherosclerosis is thought to be secondary to an immune response in the arteries and/or the effects of corticosteroid therapy. It is well known that corticosteroid therapy may induce a variety of coronary risk factors, including hypertension, hyperlipidemia, and diabetes mellitus. Attempts to minimize the corticosteroid dosage in lupus patients should be stressed. It is conceivable that alternate-day regimens may decrease the risk of coronary artery disease. This

assumption is reasonable since the diabetes mellitus and hypertension that can be induced by daily steroid administration to children with SLE decrease on alternate-day regimens.[31] Normalization of blood pressure and perhaps cholesterol levels may be important in preventing coronary artery disease in patients with SLE.[32]

Endocarditis

Libman and Sacks are credited with the early descriptions of verrucous vegetations found on the valves of lupus patients.[57] These vegetative lesions, found at autopsy, were the original pathognomonic diagnostic criteria of SLE. The verrucae may appear as pea-sized, flat or slightly raised, granular gray or pinkish projections, densely adherent to the endocardium. They occur most frequently at valve rings and commissures, and spread over both valve surfaces, valve pockets, and even onto atrial and ventricular mural endocardium, chordae tendineae, and papillary muscles. Microscopically, the vegetations consist of proliferating and degenerating cells, fibrin, fibrous tissue, and occasional hematoxylin bodies. There may be variable amounts of inflammation with a mild scattering of plasma cells and large mononuclear cells.[33] The diagnosis of Libman-Sacks endocarditis is primarily made at autopsy. Bulkley and Roberts found evidence of endocarditis in 50% of autopsied patients.[44] The mitral valve is most commonly involved, especially the recess between the posterior mitral valve leaflet and ventricular wall. Only unusually large verrucous lesions may be visualized clearly on echocardiograms.[33] The incidence of Libman-Sacks endocarditis has declined in the past 30 years, possibly secondary to steroid therapy. Most authors believe that lupus endocarditis is usually clinically insignificant. The lesions are rarely reported to cause valvular dysfunction and consequently the diagnosis of Libman-Sacks endocarditis has been established almost exclusively at necropsy.[58] Peripheral embolization, infective endocarditis, and severe valvular insufficiency have been reported, but are uncommon.[32]

Hemodynamically, significant regurgitant lesions may affect the aortic or mitral valve in SLE.[33,58] Aortic insufficiency is the most common serious problem and may be due to multiple causes in addition to verrucous endocarditis, including valvulitis, fibrosis, mucoid degeneration and fenestrations, bacterial endocarditis, and aortic dissection.[33] Hemodynamically significant mitral regurgitation is less common and has been attributed to thickening and calcification of the mitral valve leaflets, chordae tendineae scarring, fibrosis, fibrinoid necrosis of papillary muscles, and rupture of chordae tendineae.[33]

Conduction Abnormalities

High grade AV block and life-threatening arrhythmias have been reported in young patients with SLE but are uncommon.[59–61] The causes of these lesions include vasculitis of the arteries near the sinus and AV nodes and bundle of His and extension of the inflammatory lesions of myocarditis to involve the cardiac conduction system. There are many similarities to the pathologic findings seen in neonatal lupus erythematosus (see the section on neonatal lupus erythematosus).

Pulmonary Hypertension

Pulmonary hypertension has been reported to be a major clinical manifestation in some patients with SLE.[62–64] One study suggested that development of pulmonary hypertension during the course of SLE is usually associated with a significant degree of pulmonary parenchymal involvement.[62] In some patients in this study, however, the degree of pulmonary hypertension observed was disproportionate to the degree of parenchymal involvement present, suggesting a pathogenetic mechanism involving the pulmonary arteries. The clinical response to vasodilator and corticosteroid therapy is not always favorable.[62,63]

DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

It is well recognized that SLE may occur after the ingestion of certain drugs. The clinical criteria for the diagnosis of drug-induced lupus are the same as those for the diagnosis of SLE.[21] The following are additional requirements.[65]

1. A drug must have been administered before the onset of any sign or symptom used as one of the criteria for the SLE diagnosis.
2. The disease process must reverse itself promptly upon cessation of drug treatment. Clinical signs and symptoms must begin to clear within days; serologic findings may persist for months. Patients who develop lupus while receiving anticonvulsants may not always enter complete and permanent remission after the cessation of the drug. In the few cases where it has been tried, resuming the drug therapy seems to result in prompt recrudescence of the symptoms. One must question whether the convulsive disorder may actually have been the first evidence of spontaneous SLE.

The course of drug-induced SLE depends on how long the drug is administered after the symptoms first appear.[65] In general, symptoms increase in variety and severity with continuation of the inducing agent. In general, the clinical picture of drug-induced SLE differs little from that of the spontaneously occurring disease. Patients with drug-induced lupus may have a lower incidence of nephritis and a higher incidence of pleural and pulmonary involvement than that reported in spontaneous SLE.[66] It also appears that pericardial tamponade is more frequent in the drug-induced disease than in spontaneous disease.[34,35] One must differentiate between the induction of antinuclear antibodies in the asymptomatic patient and true drug-induced SLE.

Classification of Lupus-Activating Drugs

The more than 40 drugs now associated with SLE have been categorized according to the strength of conviction about their ability to cause symptoms that conform to the standard diagnostic criteria[67] (Table 88–2). The ''definite'' category includes drugs with proven ability to cause SLE, not simply to cause a positive antinuclear antibody (ANA) test with no, or only a few, lupus symptoms, to exacerbate existing SLE, or to be mistaken for the cause of pre-existing SLE. This category includes only three drugs: procainamide, hydralazine, and isoniazid. The ''possible'' and ''unlikely'' categories include drugs that have been sporadically associated with SLE but have not been confirmed in prospective studies to have a causal rather than a correlational relationship. These drugs may well produce an SLE-like syndrome, but there is simply not enough objective evidence to justify their inclusion in the ''definite'' category.

Procainamide may be the most potent drug in the group. Be-

Table 88–2. Drugs That May Induce Systemic Lupus Erythematosus*

Definite	*Possible*	*Unlikely (but Implicated)*
Hydralazine	Phenytoin	Methysergide
Procainamide	Mephenytoin	Gold salts
Isoniazid	Trimethadione	Allopurinol
	Primidone	Phenylbutazone
	Ethosuximide	Oral contraceptives
	Methyldopa	Reserpine
	Quinidine	Chlorthalidone
	Propylthiouracil	Tetracycline
	Methylthiouracil	Streptomycin
	Nitrofurantoin	Griseofulvin
	Lithium carbonate	Sulfonamides
	Penicillamine	Captopril
	Chlorpromazine (and other phenothiazines)	Cimetidine
		Practolol
		Atenolol

*Modified from references 67 to 77.

tween 15 and 100% of patients taking this drug will develop ANAs within one year, and 5 to 30% will develop drug-induced SLE.[67] Symptoms in most cases develop only after continuous administration of drug for 3 months to 2 years.[65] Hydralazine is the next most potent drug, inducing antinuclear antibodies in 24 to 50% of patients and symptoms of drug-induced SLE in 8 to 13% of cases.[67] For both of these drugs, the larger the daily dose or total dose, the more likely will be the development of drug-induced SLE. In an adult, 400 mg per day or more of hydralazine or 1.25 mg per day of procainamide is associated with an increased frequency of positive ANAs and/or lupus symptoms.[67]

Hydralazine is metabolized largely by acetylation in the liver. A genetically controlled polymorphism exists in the hepatic acetyltransferase responsible for detoxification. Individuals are classified as either slow or fast acetylators. Slow acetylators are more likely to develop positive ANAs and lupus-like symptoms.[65] Isoniazid is also acetylated by the liver, and slow acetylators are more likely to develop drug-induced lupus. Procainamide is metabolized similarly. Thus, at least for these drugs, patients in whose circulation undetoxified drug remains longer are at higher risk for developing disease.

Methyldopa has not been placed on the list of definite drugs implicated in drug-induced lupus. While it has been reported to cause SLE in a few patients, it appears to induce antinuclear antibodies in a significant number of asymptomatic patients. It more frequently causes a positive Coombs' test and hemolytic anemia.[66]

Diagnosis of Drug-Induced Lupus

Antinuclear antibodies are found in every patient with drug-induced lupus. The titer does not have diagnostic importance. The pattern is usually homogeneous or speckled. The antibodies are directed largely against histones, which accounts for the homogeneous pattern. The histones are distributed in the nucleus in a "speckled" pattern.[67] Although antihistone antibodies are strongly associated with drug-induced disease, they are also frequently seen in patients with spontaneous SLE.

The diagnosis of drug-induced lupus depends on the recognition of the ingestion of a drug known to induce the disease. Symptoms of the disease should abate quickly after discontinuation of the medication. The diagnosis of SLE secondary to anticonvulsant drugs is difficult. Seizures are a well-recognized manifestation of SLE; thus, it must be questioned whether the child who develops seizures and is treated with an anticonvulsant drug and later manifests signs of SLE has spontaneous or drug-induced SLE.

Although there have been no reports of infants with congenital complete AV block born of mothers with drug-induced SLE (this form of SLE is associated with an anti-histone rather than La or Ro), consideration should be given to discontinuing the offending therapy during pregnancy, if possible.

Management of Drug-Induced Lupus

Once a drug is suspected of causing drug-induced lupus, attempts to discontinue its administration should be made. If the clinical manifestations do not disappear promptly or are disabling, NSAIDs may be given. Corticosteroids are sometimes necessary for the pleuropericardial symptoms. The continued presence of antinuclear antibodies in the serum after the clinical manifestations of disease have disappeared should be expected; treatment should not be given for the presence or persistence of ANAs in the absence of clinical disease. If a patient has ANAs but no symptoms, the drug does not need to be withdrawn, since SLE does not develop in the majority of these patients.

The use of these potential disease-inducing drugs is not necessarily contraindicated in the treatment of patients with spontaneous SLE. One needs to consider the risk–benefit ratio and spectrum of therapeutic choices available. If these drugs are to be used in patients with SLE, one must watch closely for the exacerbation of the disease.

NEONATAL LUPUS ERYTHEMATOSUS

Neonatal lupus erythematosus (NLE) is a disease of infants characterized by congenital AV block and/or transient cutaneous lesions, often associated with hepatic or hematologic abnormalities. McCuiston and Schoch[78] are credited with the first report of NLE. Many of the early descriptions involved children of mothers with overt connective tissue disease, but it is now recognized that many mothers are asymptomatic or have mild symptoms of sicca syndrome or other connective tissue diseases.

Clinical Presentation of NLE

Lupus manifestations in the neonate can be divided into five categories.[79] (The numbers in parentheses represent approximate relative frequencies of the affected population.[80])

1. Infants with transplacental passage of antibodies, resulting in serologic markers of lupus such as LE cells, antinuclear antibodies and even occasionally low serum complement without symptoms. The exact frequency of these findings is unknown since they have not been systematically studied.
2. Infants with Coombs'-positive hemolytic anemia, thrombocytopenia, and/or leukopenia with or without skin lesions (15%).
3. Infants with skin lesions without other manifestations (26%).
4. Infants with skin lesions and other symptoms, including heart disease (15%).
5. Infants with congenital complete AV block without other signs of SLE (44%). It is emphasized that infants in this group, if their mothers are seropositive, have NLE.

Dermatologic Manifestations of NLE

Skin lesions in NLE may be present at birth, but usually develop within the first 3 months of life and usually resolve by 6 to 12 months.[81–83] There is a predilection for sun-exposed areas, especially the face, scalp, and neck, and initial lesions may suggest seborrheic dermatitis or tinea corporis. Individual lesions may rapidly develop into disk- or geographic-shaped erythematous macules, papules, or plaques, with a distinct margin separating normal skin from the lesions. Follicular plugging, hypo- or hyperpigmentation, telangiectasia, atrophy, and scarring may occur but are not usual features. The lesions may resemble the discoid lesions seen in older children and adults with SLE. Biopsy specimens of active skin lesions show the pathologic features of lupus, which include plugging of the hair follicles, focal liquification and degeneration of the basal cell layer of the epidermis, edema, and a patchy mononuclear cell infiltrate in the dermis.[82] Immunofluorescent staining of skin lesions may be positive for complement, IgM, or IgG at the dermo–epidermal junction.[82] A majority of lesions become polycyclic and appear to be identical to the lesions initially described by Sontheimer et al. in the syndrome of "subacute cutaneous lupus erythematosus."[84]

Hematologic Manifestations of NLE

Transient Coombs'-positive hemolytic anemia, thrombocytopenia, and/or leukopenia have been described in infants with NLE.[80,85] These manifestations are most likely secondary to transplacental passage of maternal IgG antibodies directed against red blood cells, platelets, and/or white blood cells.[86,87]

Cardiac Manifestations of NLE

Congenital AV block is the most serious complication of NLE and has been described in more than 100 infants with the disease.[80–82,85,88–89] Most of the cases of congenital AV block were diagnosed near the time of birth. In one study, 36 of 38 cases of AV block were diagnosed within three months before or after birth.[93] The AV block ranged from partial to complete. The location of the block is thought to be in the region of the atrioventricular node, as evidenced by narrow QRS pattern and a ventricular rate that varied between 45 to 60 beats per minute.[92] A cardiomyopathy has also been recognized in a number of these infants.[92,99,100] Postmortem studies of hearts of infants with isolated congenital AV block have revealed fibrosis and calcification along the ventricular portions of the conduction system.[88,92] A discrete atrioventricular node and/or bundle of His are often unrecognizable, replaced by elastic, fibrous, or adipose tissue and by venous channels.[88,92,93] The pathologic findings are not restricted to the conduction system. Autopsies in a few patients have revealed extensive myocardial fibrosis,[88,89,92] and in at least one reported case, fibrosis of the liver, spleen, kidneys, and adrenals.[88] Both Litsey et al.[98] and Taylor et al.[99] demonstrated antibody deposition in atrial tissue, providing strong evidence that antibodies transmitted placentally may act directly on cardiac tissue to produce complete AV block.

Systemic Manifestations of NLE

Transient elevation of liver function tests,[83,85] which may be associated with hepatomegaly, pneumonitis,[83] and urinary tract abnormalities,[85] have been described.

Sex Incidence

Previous reports suggested a preponderance of females among NLE infants with cutaneous disease (female:male ratio, 9:1)[81] and less so among those with congenital AV block alone (female:male ratio, 1.6:1).[80] Watson et al.[83] have suggested that with the addition of several more cases, susceptibility between the sexes is equal, suggesting that the clinical expression in NLE is not sex hormone–dependent.

Serologic Abnormalities

The Ro antibody system was first reported by Clark et al. in 1969.[101] The Ro title was taken from the surname of a patient who had a syndrome clinically consistent with SLE but who had a negative antinuclear titer. This patient's serum showed a unique precipitin antibody that reacted against a cytoplasmic extract of human spleen, later found to be a soluble tissue ribonucleoprotein. Later, Alspaugh and Tan[102] showed that patients with Sjögren's syndrome possess antibodies to a nuclear antigen SSA. Further studies revealed that the Ro and SSA systems were immunologically identical.[103] A related antigen—La—was found similarly to be identical to SSB. It is of great importance that most of the mothers of infants with neonatal lupus possess antibodies to this Ro/SSA antigen regardless of whether the mother was symptomatic with a connective tissue disease.[81–83,93,94,98] This antibody is found in most infants with NLE in the neonatal period, but is absent after 6 months of age, suggesting maternal transplacental transfer of this IgG antibody. It has been suggested that maternal antibody to Ro might serve as a marker to identify women at risk of having an infant with congenital AV block.[92] Circulating anti-Ro antibodies alone are not sufficient to cause the disease, as not all mothers who are Ro antibody–positive will give birth to affected infants. Some studies suggest that 5% or fewer of the infants exposed to maternal Ro antibody subsequently have features of neonatal lupus.[83] Routine fluorescent ANA testing of mothers is not sufficient, as the Ro antibody is not detected when mouse or rat tissue is used as the substrate of ANA testing. One must use human tissue as the substrate and this is not routinely used for ANA testing. The frequency of the La (SSB) antibody in NLE infant/mother pairs is also noteworthy.[83] Provost et al. recently

reported two cases of NLE characterized by the absence of anti-Ro or anti-La antibodies but the presence of anti-U_1 RNP antibodies, in the infants and their mothers.[104]

HLA Studies

In NLE, a disease in the mother characterized by autoantibody production results in clinical expression involving several organ systems in her infant. This has prompted a number of studies investigating the genetic influences on autoantibody production and clinical expression of a disease. Lee et al. have examined the HLA phenotype of six families with infants with NLE.[81] They found a significant association with HLA-DR3 in the mothers, but not in the affected infants. Lockshin et al. found similar results,[95] while Lumpkin et al. found that two of three infants and mothers studied carried the DR3 phenotype.[105] Of further interest was the increased frequency of HLA-B8, -MB2, and -MT2 phenotypes in NLE mothers.[81,83] These antigens are known to be in linkage disequilibrium, or to cross-react, with HLA-DR3. No association was found between these HLA antigens and expression of disease in infants. The finding of an association with HLA-DR3 and other linkage HLA antigens in mothers, but not in infants, supports the concept that autoantibody production is related to genetically determined products of the major histocompatibility complex. Watson et al. hypothesized that the presence of certain HLA phenotypes (notably DR2) may protect against complete clinical expression of this disease in the neonate.[83]

Risk of Development of NLE in Siblings

Despite the consistency of disease symptomatology and/or serology in the mother, the expression of disease can vary in the infants involved. Both Scott et al.[93] and Callen et al.[106] described dizygous twins with discordant disease expression of NLE; one twin had NLE, and the other was apparently unaffected. A review of the literature by Lanham et al. revealed that eight of 42 (19%) of siblings of 32 NLE probands had congenital AV block.[96] In a recent study, 25% of subsequent live births had NLE.[97] Disease expression in siblings may also vary in severity.[88] It appears that the rate of miscarriages or still births may be increased in these mothers.[93]

Etiology

It is unclear whether the atrioventricular node in NLE infants with congenital AV block is destroyed, fails to develop appropriately, or is prevented from joining the bundle of His by connective tissue interference. Evidence from postmortem studies raises the possibility of at least two hypotheses to explain the congenital AV block in these infants.

First, it is known that the atrioventricular node originates in the third to fourth week of gestation separately from the bundle of His and subsequently joins it. An injury may occur early in gestation during a critical period of organogenesis, with the embryonic nodal anlage failing to form a compact atrioventricular node and establish normal relations to the interatrial septum and annulus. The inability to find a discrete atrioventricular node and/or bundle of His may support this theory.[88,92,93] IgG antibodies can cross the placenta as early as 12 weeks of gestation and could potentially interfere with cardiac embryogenesis. Neither IgA nor IgM can cross the placenta, and their presence in fetal tissues would suggest fetal production of these antibodies. The finding of IgA[98] and IgM[99] deposition raises the additional possibility that cardiac tissue damaged by maternal antibody or an as yet unknown substance may be rendered immunogenic in the fetus, with the subsequent production of IgA and IgM antibodies.

Second, a definitive atrioventricular node develops during cardiac organogenesis but is subsequently destroyed and fibrosed. An active inflammatory process occurring in the fetal atrioventricular junctional tissues could result in destruction and fibrosis of these vital areas. A number of issues support this theory.

1. The majority of maternal antibodies cross the placenta in the third trimester, thus appearing too late to interfere with embryogenesis; however, sufficient antibody is present to participate in immune-mediated inflammation.
2. When the atrioventricular node is found, it is often in a sea of dense connective tissue.[83]
3. AV block, although rare in the adult with SLE, has been described and the pathological changes associated with it are identical to those of NLE.[59–61]
4. Normal heart rate and function have been documented earlier in the pregnancy prior to the development of complete AV block.[100]
5. ECG patterns in some infants with complete AV block have demonstrated abnormal rhythms elsewhere in the heart, usually early in life, and in particular atrial flutter and premature contractions.[107]

Ro/SSA antigen has been shown to be present in the skin, heart, and other internal organs.[108] It is conceivable that anti-Ro antibodies, or another unidentified antibody system, might induce an inflammatory response preferentially affecting the richly vascular parts of the heart, including the conduction system.[83] In a study investigating the association between congenital AV block and maternal antibodies capable of crossing the placenta, Taylor et al.[99] reported that serum antibodies reactive with fetal heart tissue were present in a significantly higher proportion in mothers of infants with congenital complete AV block than in controls. These antibodies consisted predominantly of IgG and therefore were able to cross the placenta. In addition, these antibodies did not react selectively with the conduction system, but reacted with other all myocardial tissue, as well as with other fetal tissues.

One must question why the mothers of these infants are not similarly affected. These mothers almost always have serum antibodies to Ro (SSA) and to La (SSB), but the reverse is not true, suggesting additional factors are necessary to induce the pathologic conditions.[99] The finding of Ro antibody in the serum of these mothers and infants may be an epiphenomenon. Other hypotheses include the possibility that the mothers have blocking antibodies of IgA or IgM class, thereby protecting their conduction system from immunologic assault. Or, it is possible that the developing conduction system is more sensitive to immune-mediated inflammation than the mature system.

Prognosis

The prognosis of NLE in the absence of congenital AV block is excellent: the clinical and serological features disappear by 1 year of age.[83] The presence of AV block increases the mortality.[83,109] In one study, infants who survived continued to have AV block, and some had severe cardiomyopathy or associated congenital defects.[110] There have been reports that some NLE infants later developed other connective tissue diseases, including

SLE,[96,110,111] juvenile rheumatoid arthritis,[91,107] or Sjögren's syndrome,[96] but this appears to be unusual.

Management of Mothers and Infants with NLE

Mothers suspected of having infants with NLE should be monitored closely during pregnancy for signs of fetal bradycardia or fetal distress. Buyon et al.[100] reported the successful treatment with dexamethasone and plasmapheresis in a mother whose fetus abruptly developed AV block and myocarditis. At birth, there was no evidence of myocarditis, although there was evidence of AV block. Herreman and Galezowski, however, reported less successful results with steroid therapy and plasmapheresis, although therapy was not instituted until after 23 weeks when there was already evidence of fetal bradycardia.[112] Currently, there are no clear cut recommendations for treatment of these mothers during pregnancy. The asymptomatic mothers should be monitored for later development of connective tissue diseases, most notably SLE, rheumatoid arthritis, or Sjögren's syndrome. In a recent study, half the mothers were initially asymptomatic despite having anti-Ro antibodies. When followed for a mean of 4.5 years, 18 of 21 mothers developed symptoms of connective tissue disease.[97]

Infants with NLE should avoid unnecessary exposure to ultraviolet light, as this may exacerbate or trigger the cutaneous disease.[83] In most cases, no therapeutic intervention is necessary for the skin disease as most of the lesions will disappear spontaneously. Infants with complete AV block may require pacemakers. The AV block is virtually always permanent. The hematologic abnormalities usually resolve spontaneously as the maternal antibodies disappear, but may require transfusion therapy.

SPONDYLOARTHROPATHIES

The term *spondyloarthropathy* refers to a spectrum of seronegative arthritic diseases consisting of ankylosing spondylitis, juvenile ankylosing spondylitis, the spondylitis of inflammatory bowel disease, Reiter's disease and several other postinfectious arthropathies, and psoriatic arthritis. They are termed "seronegative" because the rheumatoid factor is consistently absent from the sera of affected patients. While patients with these diseases may demonstrate peripheral arthritis, the hallmark of these diseases is arthritis of the axial skeleton.

Ankylosing spondylitis is perhaps the best described spondyloarthropathy.[113] The disease is characterized by pain, stiffness, and loss of mobility of the back. The distribution of the pathologic changes in ankylosing spondylitis follows a characteristic pattern. The primary site of this inflammatory disease is the insertion of ligaments and capsules into the bone, or the enthesis; hence the term enthesopathy. The major target appears to be the joints of the axial skeleton, including 1) the nonsynovial (cartilaginous) synchondroses of the intervertebral spaces; 2) the diarthrodial synovial joints (apophyseal and costovertebral articulations); and 3) the sacroiliac joints, which possess features of both nonsynovial and diarthrodial articulations. Inflammation of the peripheral joints also occurs, with the hip, knees, and shoulders primarily involved. The major target tissue of inflammation is cartilage, especially fibrocartilage. There is often an associated osteitis of the directly adjacent subchondral bone. In 80% of patients, initial complaints are usually referable to the sacroiliac joints and low back and consist of pain and stiffness in the low back, buttocks, thighs, and hips.[114] These symptoms are often transient and recurrent for years before obvious loss of spinal mobility occurs. In about 20% of patients, the disease begins with arthritis of peripheral joints, and in about half the patients peripheral joints are affected at some time during the course of the disease.[114] Diagnosis is based on the clinical picture and the presence of characteristic radiographic changes of the sacroiliac joints.[115] Ankylosing spondylitis is usually considered to be a disease that affects young adult males. It had been recognized for years that ankylosing spondylitis often occurs in families. The search for the explanation of this increased family prevalence took a dramatic step forward in 1973 when two reports defined the association of the genetic marker, HLA-B27, with ankylosing spondylitis.[116,117] HLA-B27 is found in approximately 90% of Caucasian patients with ankylosing spondylitis, as opposed to 8% of the general Caucasian population.

Ankylosing spondylitis has been described with a childhood onset.[114,118,119] In childhood it may be present with axial symptoms, similar to its presentation in adults. Or it may begin in childhood with peripheral arthritis, often misdiagnosed as pauciarticular juvenile rheumatoid arthritis. It may take several years before sacroiliac and spinal involvement becomes apparent. It is commonly believed that children in whom ankylosing spondylitis subsequently develops are usually boys, with pauciarticular or lower limb arthropathy (especially hip or hip girdle), whose disease onset occurs in late childhood, usually older than 8 years of age. These children are usually negative for rheumatoid factor or ANAs. However, as is true of adults, the vast majority are positive for HLA-B27.[120] The diagnosis is often delayed because of the rate of appearance of characteristic radiographic changes.[121] Both adults and children with ankylosing spondylitis may develop acute iritis.

In patients with ulcerative colitis and Crohn's disease, the rate of ankylosing spondylitis is higher than in the general population.[122–124] This spondylitis is different than the peripheral arthritis seen in patients with inflammatory bowel disease. This latter form of arthritis is usually associated with active disease, may be accompanied by erythema nodosum or pyoderma gangrenosum, and generally follows the course of the underlying disease, that is, when the colitis is cured, so is the acute arthritic problem. The spondylitis associated with inflammatory bowel disease is associated with the presence of HLA-B27 and follows its own course, often continuing after the colitis is eliminated.

A reactive arthropathy is an inflammatory arthritis in a patient who recently had an infection that did not involve microbial invasion of the joint space.[125] Again, most of the patients with reactive arthritis are HLA-B27 positive. The infectious agents most responsible include Shigella, Salmonella, Yersinia, and Campylobacter. These patients may present with fever, polyarticular arthropathy, and erythema nodosum. The symptoms may mimic those of acute rheumatic fever.

A classic form of postinfectious acute arthropathy is Reiter's syndrome.[125] Urethritis, conjunctivitis, and arthritis were once considered the classic triad. Buccal ulceration, balanitis, cervicitis, and keratoderma may also be part of the clinical picture. Rheumatologic features include arthralgia, tenosynovitis, plantar fasciitis, and other enthesopathies, as well as frank arthritis. Typically, the digits become sausage-shaped. HLA-B27 is present in 80% of patients with Reiter's syndrome and may follow dysenteric or venereal infections, especially Shigella and Chlamydia.

Cardiovascular Manifestations of the Spondyloarthropathies

Aortic Insufficiency

Like ankylosing spondylitis, acquired aortic regurgitation is predominantly a disease of adult males.[126] In children it is usually a sequela of acute rheumatic fever; less commonly it is the result of bacterial endocarditis or associated with Marfan's syndrome.

The association between aortic insufficiency and ankylosing spondylitis was originally described by Bauer et al.[127] The prevalence of aortic insufficiency increases with the duration of the spondylitis, occurring clinically in up to 10% of patients after 30 years and as high as 20% in postmortem studies.[127–131] In some patients, however, aortic regurgitation was present before distinctive radiologic changes of ankylosing spondylitis became apparent.[130]

Bulkley and Roberts[130] described the characteristic pathology of aortic regurgitation in ankylosing spondylitis. Their findings included cellular proliferation and scar formation resulting in a shortening and thickening of the aortic valve cusps, as well as a subaortic fibrous ridge or "bump." Scar tissue may extend into the subaortic area and infiltrate the membranous and muscular septum, producing mitral insufficiency and affecting the conduction system with resultant rhythm disturbance and AV block.[130,132–137]

Cardiac manifestations similar to those described in adults are relatively uncommon in juvenile ankylosing spondylitis.[126,138–141] Reid et al.[126] described a 9-year-old boy who developed restricted back mobility followed by severe peripheral arthritis. One year later, aortic insufficiency was detected. His cardiac lesion apparently was not progressive. Gore et al.[138] described a patient with the onset of peripheral arthritis at the age of 9 years, followed 2 years later by the development of aortic regurgitation and carditis. Six months later sacroiliac involvement was noted. One year later aortic insufficiency developed. Kean et al.[139] described a 15-year-old boy with severe polyarticular peripheral arthritis and uveitis who developed mild aortic regurgitation 1 year after the onset of arthritis. In 10 years of followup, the cardiac lesion had not progressed, peripheral arthritis had remitted, and sacroiliitis had not appeared. Stewart et al.[140] described a 16-year-old boy initially seen with severe aortic and mitral regurgitation who developed spondylitis and iridocyclitis 5 and 6 years later, respectively, as well as mild peripheral arthritis. Pelkonen et al.[141] described a 13-year-old boy with arthritis. A cardiac murmur was heard 15 months after the onset of the articular symptoms, and 8 months later the patient required surgery because of massive aortic regurgitation. Radiographic evidence of sacroiliitis was not detected until almost 4 years after the onset of his joint symptoms. In these five patients, there was no correlation between the type of joint presentation (peripheral arthritis versus root joints versus sacroiliitis) and the development of cardiac lesions. There was also a discrepancy in the severity of cardiac involvement among these patients. The presence of HLA-B27 was the only consistent feature. Aortic insufficiency has also been described in a young boy 32 months after the onset of Reiter's syndrome.[142] The apparent lower frequency of cardiac involvement in juvenile ankylosing spondylitis may reflect the fact that followup is of shorter duration than in adults. It seems prudent to advise that all children with a spondyloarthropathy be followed closely for the development of aortic insufficiency as they progress into adulthood.

Conduction Defects

Atrioventricular conduction disturbances occur in ankylosing spondylitis and are often associated with aortic valvular disease.[128–137] Weed et al.[132] estimated that 44% of ankylosing spondylitis patients with aortic insufficiency will have cardiac conduction defects, while 8% of ankylosing spondylitis patients without aortic insufficiency will have conduction defects. In any event, conduction defects appear more frequently in patients with ankylosing spondylitis than in the general population. Some studies suggest that the frequency of heart disease is greater when the spondylitis is severe and accompanied by peripheral arthritis or iritis,[128] while other studies suggest that heart disease can appear as a late manifestation of mild uncomplicated disease.[132] Conduction disturbances are rare in children with juvenile ankylosing spondylitis. Pelkonen et al. described a young patient with progressive lengthening of the P-R interval and rapid progression of aortic regurgitation.[141] The pathologic basis for the conduction disturbance in patients with ankylosing spondylitis is thought to be a result of extension of the fibrous process extending from the aortic root and valves and membranous ventricular septum into the muscular septum to interrupt or destroy the conduction fibers in the atrioventricular bundle or proximal bundle branches.[120,137] Some authors believe that electrocardiographic evidence of a conduction defect may provide an early indicator of aortic root disease.[132,141]

Conduction disturbances have also been described in patients with Reiter's syndrome.[143,144] First-degree heart block is the most common disturbance detected. It is usually transient and occurs during the active phase of illness. Some conduction abnormalities, however, appeared after a long latent period at a time when other manifestations of Reiter's syndrome were inactive. Complete AV block is a rare manifestation of this disease, and when it occurs it is usually after a long course of recurrent arthritis, iritis, urethritis, and dermatologic abnormalities. As in patients with ankylosing spondylitis, aortic regurgitation is often associated with complete AV block in Reiter's syndrome.

While conduction disturbances are rare in children with spondyloarthropathies, regular evaluations with electrocardiograms as they progress to adulthood may warn of future valvular involvement.

LYME DISEASE

In 1975, an epidemic form of pauciarticular arthritis was recognized in Old Lyme, Connecticut.[145] The disease is now known to be a complex multisystem disease involving the skin, joints, nervous system, and heart. It usually begins in summer with erythema chronicum migrans (ECM), the unique clinical marker for Lyme disease. The lesion begins as a red macule or papule that expands to form a large, annular lesion, usually with a bright red outer border, partial central clearing, and indurated center.[146] The lesion may occur anywhere, but the thigh, groin, and axilla are particularly common sites. The lesion resembles an arthropod bite. Within several days after the appearance of the initial skin lesion, many patients develop multiple annular secondary lesions. Skin involvement is often accompanied by systemic manifestations, including malaise, fatigue, fever, chills, generalized achiness, and regional lymphadenopathy.[146,147] In addition, some patients may have evidence of meningeal irritation, mild encephalopathy, mi-

grating musculoskeletal pain, hepatitis, generalized lymphadenopathy or splenomegaly, sore throat, nonproductive cough, or testicular swelling.[148]

Neurologic manifestations may appear while ECM is present or several weeks after it fades, and may include aseptic meningitis, encephalitis, chorea, cerebellar ataxia, cranial neuritis (including bilateral facial palsy), motor and sensory radiculoneuritis, mononeuritis multiplex, and myelitis.[149]

About 60% of patients develop arthritis within a few weeks to years after the onset of illness.[146] Early in the illness, patients may complain of migratory musculoskeletal pain, often without actual joint swelling. The arthritis does not usually appear until months to years later. It is at this time that patients are often misdiagnosed as having juvenile rheumatoid arthritis, especially if the early symptoms are not recalled.

Cardiac Manifestations of Lyme Disease

In patients with Lyme disease, the incidence of cardiac involvement has been estimated to be 8%.[150] Steere et al.[151] described 20 patients with Lyme carditis. The most common finding was atrioventricular block, including 10 patients with high degree AV block (complete in eight, Wenckebach in two) and eight patients with first-degree block. All patients with high degree AV block were symptomatic with syncope, dizziness, shortness of breath, and/or chest pain. The degree of AV block often fluctuated rapidly; in all patients with complete AV block, first-degree and Wenckebach-type second-degree block were also seen. Some patients went from first-degree to complete AV block and back within minutes. In all patients, the AV block appeared proximal to the bundle of His. Some patients have evidence of more diffuse cardiac involvement, including electrocardiographic changes compatible with acute myopericarditis, radionucleotide evidence of myocarditis, or, rarely, cardiomegaly, pleural effusions, or pancarditis.[151–153] The duration of cardiac involvement is usually brief (3 days to 6 weeks), but it may recur.[148] Some patients have required temporary transvenous pacemakers.[153] On rare occasions, Lyme carditis may occur in the absence of other clinical symptoms.[154]

Laboratory Findings

Etiologic Agent

Lyme disease is now known to be caused by a newly recognized spirochete that has characteristics of both treponemes and borreliae,[155,156] and has been named Borrelia burgdorferi.[157] It is transmitted by the tick Ixodes dammini. The organism has been recovered from skin, cerebrospinal fluid, joint fluid, and cardiac myocardium from patients with Lyme disease.[153,155–158] The principal endemic areas are the coastal northeast and western states, Minnesota and Wisconsin; however, cases have been reported in other states as well as in Europe. The peak onset is usually in the summer. The principal animal hosts for the tick are mice and deer.

Antibody Titers

Specific IgM antibody titers against the I. dammini spirochete usually reach a peak between the third and sixth week after the onset of disease; specific IgG antibody titers rise slowly and are generally highest months later, when arthritis is present.[155] The presence of antibody titers against this spirochete are useful in differentiating Lyme disease from other rheumatic illnesses.

Other Laboratory Findings

Early in the course of the illness the sedimentation rate is usually elevated.[146,147] Liver function tests may be abnormally elevated, especially when ECM is present.[147] Circulating immune complexes are present in most cases at the onset of ECM and may persist in patients with subsequent nerve or heart involvement.[159] In contrast, in patients with only subsequent arthritis, immune complexes usually disappear from the serum within 3 months. The finding of elevated serum IgM levels and cryoglobulins containing IgM may predict subsequent nervous system, cardiac, or joint involvement.[160]

Differential Diagnosis of Lyme Disease

ECM is the unique clinical marker for Lyme disease and, when present in its classic form, is diagnostic of Lyme arthritis.[148] The lesion, however, does not always take on its classic appearance or may be forgotten by the time subsequent sequelae of the disease appear.

The early manifestations of Lyme disease (especially severe headaches and stiff neck, abdominal symptoms, and lymphadenopathy) may be confused with viral infections, especially when ECM is absent or missed or is not the first manifestation.[148]

The later manifestations may be confused with several immune-mediated illnesses. Acute rheumatic fever should be considered in the differential diagnosis.[151] The Jones' major clinical criteria for rheumatic fever include carditis, arthritis, chorea, erythema marginatum and subcutaneous nodules. Except for erythema marginatum, which superficially resembles ECM, the remaining manifestations may be seen in both rheumatic fever and Lyme disease. The carditis of Lyme disease, however, affects adult men more frequently than children, and, in addition, does not usually affect the valves. The most frequent cardiac involvement in Lyme disease is complete AV block with mild myopericardial involvement. The arthritis may be similar in Lyme disease and rheumatoid arthritis, but commonly recurs for several years in Lyme disease. An important distinction between these two diseases is the possibility of other neurologic involvement (headache, stiff neck, frank meningoencephalitis) that may accompany cardiac involvement in Lyme disease.

Children with chronic arthritis are often misdiagnosed as having juvenile rheumatic arthritis (JRA); however, several distinctions may be made. The classic picture of ECM and the rheumatoid rash of JRA are dissimilar. While complete AV block is the most common cardiac manifestation of Lyme disease, it is an extremely unlikely accompaniment to JRA. Instead, pericarditis is the most common cardiac manifestation of JRA (see the section on JRA).

Yersinia enterocolitica may cause valvulitis, myopericarditis, and polyarthritis and may be confused with Lyme disease.[151] Unlike Lyme disease, however, diarrhea and abdominal pain are characteristic, cardiac conduction abnormalities are unusual, and the only associated skin manifestation is erythema nodosum.

Treatment of Lyme Disease

ECM responds promptly to therapy with penicillin or tetracycline.[151] Steere and Malawista[148] recommend that when patients are early in the course of illness, adults receive oral tetracycline, 250 mg four times a day for at least 10 days. Phenoxymethyl penicillin, 500 mg four times a day for the same duration, or 2.4 million units of benzathine penicillin intramuscularly may be as

effective. In children, they recommend phenoxymethyl penicillin, 50 mg per kg per day (not less than 1 gram per day or more than 2 grams per day) in divided doses for 10 to 20 days, or in the case of penicillin allergy, erythromycin, 30 mg per day, in divided doses for 15 or 20 days.

In patients with frank meningitis, spinal pleocytosis, and cranial or peripheral neuropathies, they recommend intravenous penicillin G, 20 million units a day in divided doses for 10 days.[148]

Established Lyme arthritis can also be treated with high-dose penicillin.[148] Regardless of antibiotic therapy, the duration of heart involvement is usually brief. Steere et al.[151] are uncertain of the advisability of prednisone for heart involvement. Because the first patient who received it improved, subsequent patients in that study with high-degree AV block were also so treated. All had improvement in the degree of block within 24 to 48 hours, and all except one had complete resolution within 1 to 2 weeks. The major disadvantage of prednisone was that because of recurrent nervous system or joint involvement 2 to 4 months of therapy were usually needed before the medication could be stopped.

Steere et al. recommend that patients with high-degree AV block or first-degree block with PR intervals longer than 0.30 second be hospitalized because of the marked risk of developing complete AV block.[151] In patients with complete AV block they advise therapy with a temporary pacemaker and aspirin. They recommend treatment with prednisone if the patient also demonstrates meningoencephalitis, complete AV block for longer than one week, or deterioration of cardiac status with cardiomegaly.

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CHAPTER 89

Kawasaki Disease

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Michael R Nihill

Kawasaki disease was named for Dr. Tomisaku Kawasaki, who recognized and made the original report of this disease. It is a clinical entity of an acute febrile syndrome of unknown etiology, observed predominantly in children under 4 years of age. In addition to prolonged fever and exanthema, which are common clinical manifestations of the diseases of children, Kawasaki disease has been characterized by its risk of sudden death due to coronary arteritis accompanied by aneurysms and thromboembolism. With an increase in numbers of affected young children, it has become a worldwide problem.

HISTORY

In January 1961, Dr. Kawasaki saw a 4-year-old boy who had been suffering from fever persisting for 7 days. His cervical lymph nodes were swollen, minor bleeding was present from the fissurings of lips, the conjunctivae were injected, and exanthema covered his body. His palms and soles were erythematous with indurative edema. Later there was peeling (desquamation) from his fingertips. This boy was treated with penicillin and steroids. Fever subsided after 2 weeks duration and the other symptoms improved gradually. He was sent home after a 1-month hospitalization. In 1962, Dr. Kawasaki saw a total of six patients with the same clinical manifestations as the first 4-year-old boy. It was 2 to 3 years afterward that other Japanese physicians started to recognize this syndrome as a new clinical entity. Until then, it had been diagnosed as either exanthema multiforme exudativum, Stevens-Johnson syndrome, and/or juvenile rheumatoid arthritis.

In 1967, Dr. Kawasaki made a report on 50 cases of this rather unique syndrome as "febrile oculo-oro-cutaneo-acrodesquamatous syndrome with or without acute nonsuppurative cervical lymphadenitis."[1] In 1970, The Japan Mucocutaneous Lymph Node Syndrome (MCLS) Research Committee sponsored by the Ministry of Welfare was formed and the first national survey was conducted, revealing 26 in 1857 patients due to this disease, which was once thought to be benign.

The numbers of affected children continued to increase in Japan. There have been three nationwide outbreaks: in 1979 (6867 reported patients), 1982 (15,519 patients), and 1986 (12,847 patients). Although this disease is extraordinarily prevalent in Japanese infants and younger children living in Japan, cases have been increasing on a worldwide basis. In 1973, the first report of 8 cases of MCLS outside Japan was released from Korea,[2] followed by reports from the United States.[3–5] The publication by Dr. Kawasaki in an English journal[6] spread the information about this syndrome and accelerated its recognition. There have been reports from Canada,[7] Central and South America,[8] Europe,[9–12] Australia, and other countries throughout the world.[13–17]

EPIDEMIOLOGY

Incidence

According to the national epidemiologic surveys conducted in Japan, the number of the patients reached 83,857 (boys 48,570, girls 35,287) in Japan by the end of 1986, with 349 deaths (0.4%). In the United States, 2091 cases had been reported by the end of 1985.

Race

The majority of affected children have been Japanese or those with Japanese background. According to the report from the Centers for Disease Control (CDC), the incidence rate per year among children aged 8 or less living in the United States was nearly three times higher in Asian-American children than in black children, and more than six times higher in Asian-American than in white children. The incidence in Japan is greater than 40 cases per year per 100,000 children aged 4 years or less.

Sex

In Japan, the ratio of males to females of children with Kawasaki disease is about 1.4:1. Although it once had been reported as to be about 1.5:1, the numbers of affected female children have been increasing since 1979.[18] In the United States, it is about 1.67:1. Fatal cases of Kawasaki disease are also more common in males.

Age

Kawasaki disease is essentially found in infants and younger children. The youngest patient so far recognized in Japan was 35 days old at the onset. In Japan, about 1% of the patients are younger than 2 months or older than 9 years. The peak age is in the first year for both males and females.[19] In Japan and also in the United States, some adult cases have also been reported, but they are extremely rare.[3,7,20–23]

According to a recent report from Japan, 38% of deaths occur in infants 6 to 12 months of age, 68% in children less than 2 years old, and 78% in children less than 3 years old; 39% of deaths had their acute phase before 6 months of age.[18] In Japan, 349 death cases were reported by the end of 1986. There were 10 and 18 deaths in 1985 and 1986, respectively, showing the fatality rate by year of 0.1% for two consecutive years.

Geography

Kawasaki disease has been recognized worldwide and diagnosed in at least 27 countries. Next to Japan, the following countries are listed in descending order according to the numbers of recognized cases: Korea,[2] United States,[3–5] Canada,[7] West Germany, Finland, France, England, New Zealand, Australia, Taiwan, Sweden, Belgium, and the Netherlands. In all of the above countries, more than 10 cases have been reported.[18]

Season

In Japan, Kawasaki disease is seen year round. Although there were certain increases of patients from April to June in the two outbreaks in 1979 and 1982 in Japan, no clear pattern has been observed so far. In Korea, there have also been two outbreaks, from November 1979 to January 1980 and from May 1983 to September 1983.[18]

Communicability

There has been no evidence that Kawasaki disease is transmitted from person to person. In Japan, 1.5 to 2% of reported cases have been found in two siblings, and 50% of them had the disease occur within 7 days of the other.[18,24] The percentage is certainly too high to be due to chance, but at the same time, it is too low to accept as proof of an infectious etiology of this syndrome.[5] In Japan, there is a recurrence rate of 3%. One patient had the disease four times.

Clustering

In Japan and also in the United States, there has been a geographic clustering of cases, but the significance of this is still unknown. In 1979, local and temporal geographic clustering was noted starting from March in southern Japan to June in northern Japan. It is of interest to know that two outbreaks in Korea (1980, 1983) occurred approximately 1 year after outbreaks in Japan. Outbreaks have been also reported in several large American cities.[25,26]

PRESENTATION

Clinical

Diagnostic guidelines of Kawasaki disease (MCLS) were suggested initially in 1970 by the MCLS Research Committee. Since then, changes have been made. The present diagnostic guidelines are from the fourth edition revised in 1984 (Table 89–1).

High fever (approximately 39°C) is the initial symptom of this disease.[27] The fever persists for 5 or more days. The effect of antipyretics is temporary. In most of the cases, fever subsides in 1 to 2 weeks but in some cases, the patient becomes febrile again or even a third time after a 1- or 2-day afebrile period.

Erythema of the palms and soles with indurative edema of hands and feet are seen several days after the onset of fever (Fig. 89–1). Peeling or membranous desquamation of the fingertips and toes begins 10 to 15 days after the onset of the disease, when high

Table 89–1. Diagnostic Guidelines of MCLS

A. PRINCIPAL SYMPTOMS
1. Fever persisting 5 days or more
2. Changes of peripheral extremities:
   [Initial stage]: reddening of palms and soles, indurative edema
   [Convalescent stage]: membranous desquamation from fingertips
3. Polymorphous exanthema
4. Bilateral conjunctival congestion
5. Changes of lips and oral cavity: reddening of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
6. Acute nonpurulent cervical lymphadenopathy

B. OTHER SIGNIFICANT SYMPTOMS OR FINDINGS
The following symptoms and findings should be clinically considered:
1. Cardiovascular: auscultation (heart murmur, gallop rhythm, distant heart sounds), ECG changes (prolonged PR–QT intervals, abnormal Q wave, low voltage, ST-T changes, arrhythmias), chest x-ray findings (cardiomegaly), 2-D echo findings (pericardial effusion, coronary aneurysms), aneurysm of peripheral arteries other than coronary (axillary, etc.) angina pectoris or myocardial infarction
2. GI tract: diarrhea, vomiting, abdominal pain, hydrops of gallbladder, paralytic ileus, mild jaundice, slight increase of serum transaminase
3. Blood: leukocytosis with shift to the left, thrombocytosis, increased α2-globulin, slight decrease in erythrocyte and hemoglobin levels
4. Urine: proteinuria, increase of leukocytes in urine sediment
5. Skin: redness and crust at the site of BCG inoculation, small pustules, transverse furrows of the fingernail
6. Respiratory: cough, rhinorrhea, abnormal shadow on chest x-ray
7. Joint: pain, swelling
8. Neurological: pleocytosis of mononuclear cells in CSF, convulsion, unconsciousness, facial palsy, paralysis of the extremities

*With at least five of the six principal symptoms, or four associated with coronary lesions confirmed by two-dimensional echocardiography or angiography, diagnosis of MCLS can be established.

Fig. 89–1. Erythema of soles and polymorphous exanthema.

fever usually subsides (Fig. 89–2). In contrast to scarlet fever, it is restricted to the hands and feet.

A few days after the onset of fever, an erythematous rash of variable size develops predominantly over the trunk. The rash itself is not characteristic, however, it resembles that of measles of early stage (Fig. 89–3). Patients rarely complain of itching. Vesicles or crust formation are rare except for at the site of BCG inoculation. Within a few days after the onset of fever, the bulbar conjunctivae become hyperemic bilaterally (Fig. 89–4). Purulent conjunctivitis is a rare complication. The lips become reddish, dry, cracked, and sometimes hemorrhagic. A ''strawberry tongue'' appearance is usual (Fig. 89–5) and the oral mucosa is also hyperemic. By this time, when conjunctival congestion and polymorphous exanthema are also present, in most of the cases, the diagnosis of Kawasaki disease can be made. A ''toxic'' appearance of the patient with injected bulbar conjunctivae, bright red lips, and rash on the face are characteristic and impressive.

Fever for 5 or more days, polymorphous exanthema, conjunc-

Fig. 89–3. Polymorphous exanthema.

Fig. 89–2. Desquamation of the feet.

Fig. 89–4. Nonpurulent conjunctival congestion.

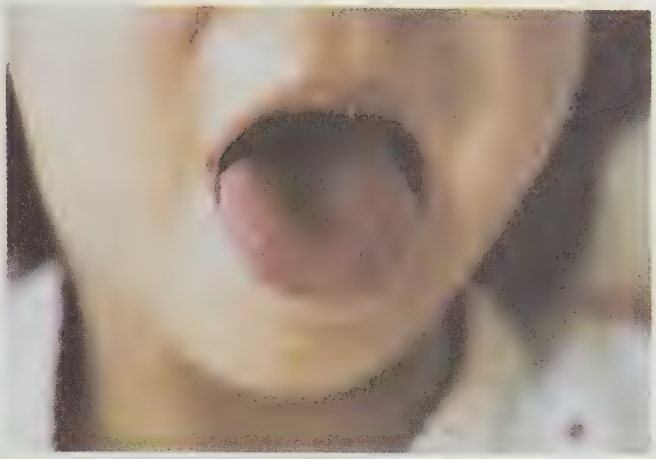

Fig. 89–5. Strawberry tongue.

tival congestion, and reddening of the lips are seen in more than 90% of patients. Nonsuppurative cervical lymphadenopathy is seen in about 70% of the cases, usually at an early stage. The lymphadenopathy is not always bilateral and may disappear quickly. Occasionally, a patient is misdiagnosed as having mumps due to the diffuse swelling of the submandibular area. Lymphadenopathy is restricted to the area around the neck.

Auscultation of the heart reveals a gallop rhythm and distant heart sounds in 80% of patients, usually in the second week of illness.[28] Rarely, a murmur of mitral regurgitation is heard. Cardiomegaly on chest roentgenography is seen in more than 30% of patients.

Watery diarrhea with mild abdominal pain and vomiting may appear in the early phases of the illness in 35% of patients. In patients with bloody stools, Yersinia infection must be ruled out as well as intussusception.[29] Frequent vomiting or meningeal signs necessitate lumbar puncture. Tenderness in the right upper quadrant could be due to a hydropic gallbladder, in which case echographic examination of the abdomen is indicated.[30–33] Reddening followed by crust formation at the site of BCG inoculation is a relatively early sign of Kawasaki disease, especially in infants within one year after the inoculation (Fig. 89–6). Sterile small pustules on or around the knees, elbows, genital area, and buttocks are occasionally seen in 3 to 10% of patients in the first to second week of illness. Large joint arthralgias and arthritis with pain and/or swelling may be noted but not frequently. Isolated facial palsy, hearing difficulty, unconsciousness, and paralysis of the extremities during the acute stage are rare complications.[34–36]

Fig. 89–6. Reddened skin at the site of BCG inoculation with small pustules.

Laboratory

Electrocardiographic changes include PR prolongation, low voltage, QTC prolongation, ST depression, and ST elevation[37,38] (Fig. 89–7). Low QRS voltage and ST depression are usually seen in the first week of illness in 6 to 43% of patients and 23 to 56%, respectively. In the second and third weeks of illness, PR prolongation, (41%), QTC prolongation (59%), and ST elevation (20%), are seen. Arrhythmias are rare and temporary. Development of paroxysmal supraventricular tachycardia, atrial fibrillation, ventricular tachycardia, and complete atrioventricular block are associated with serious coronary arterial lesions. Electrocardiographic changes are common in cases of patients with cardiomegaly, congestive heart failure, and heart murmur. An electrocardiogram should be recorded at least once per week during the acute phase of the disease.

Two-dimensional echocardiography is extremely useful to detect and follow the most serious complications of Kawasaki disease, i.e., aneurysms of the coronary arteries (see Complications, below)[39–46] (Fig. 89–8).

Leukocytosis with a shift to the left is a common finding. Leukocyte counts in excess of 20,000 per cu mm occur in about 25% of patients and in excess of 15,000 per cu mm in about 50%. Anemia occurs in about 50% of patients. The erythrocyte sedimentation rate is usually elevated as well as the $\alpha 2$-globulin level. C-reactive protein is positive in about 90% of patients. Thrombocytosis with platelet counts in excess of 500,000 per cu mm is a constant laboratory finding that develops in the second week of illness. Usually it persists for about 4 to 6 weeks. Leukocyte counts are increased in urine sediment and proteinuria is also common, but bacteria are rarely found in the urine.[4,47]

Pleocytosis of mononuclear cells in the cerebrospinal fluid (CSF) is a common finding but CSF glucose and protein are normal in almost 90% of cases. Aseptic meningitis, which usually develops within 10 days of illness when the patient is usually still febrile, is a rather frequent complication seen in 10 to 53% of

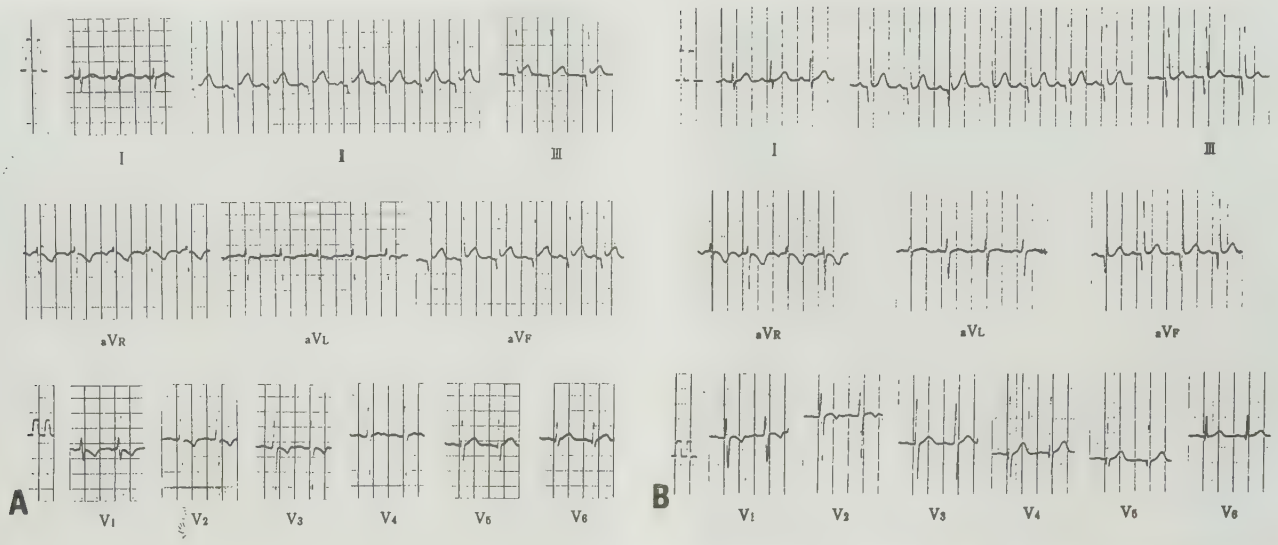

Fig. 89–7. Serial electrocardiograms of a 7-year-old asymptomatic boy who had Kawasaki disease at 5 months of age. His fever persisted for about 50 days. (A) Electrocardiogram at 2 months of illness when the patient was still febrile, reveals ST elevation in leads II, III, aVf. (B) Electrocardiogram at 3 years and 1 month reveals deep Q wave in lead III.

cases. Patients under 1 year of age are most susceptible; irritability and meningeal signs are usually mild. Electroencephalographic abnormality, i.e., diffuse slow waves, is frequently revealed in the acute state of the disease.

PATHOLOGY

The pathologic basis of this syndrome is an acute nonspecific, and systemic vasculitis. Since the majority of the victims of this disease died of coronary lesions, extensive studies have been done on the cardiovascular lesions of this syndrome and they have been classified into four stages according to the duration of illness.[48]

Stage I (days 0 to 12) is characterized by acute vasculitis of the microvessels and small arteries and by acute perivasculitis and endarteritis of the major arteries, especially of the coronary system. Stage II (days 12 to 25) is characterized by panvasculitis and aneurysm formation of the coronary arteries resulting in thrombus formation and local obstruction. In stage III (days 26 to 40), granulation of the medium-sized arteries, especially coronary arteries, and at the same time disappearance of inflammation in the microvessels and smaller arteries are evident. In stage IV (day 40 and beyond), scarring, thickening of the intima, calcification, thrombus formation, and recanalization in the major coronary arteries are noted (Figs. 89–8 and 89–9).

Arteritis is particularly severe and frequently observed in the coronary arteries[49–51] and iliac arteries, but major arterial branches of the aorta such as mesenteric, renal, celiac, subclavian, carotid, and hepatic arteries may also be involved[39–44,52] (Fig. 89–10).

Aneurysm formation in the major coronary arteries is the most characteristic finding of this disease. Clinically 10 to 20% of patients develop coronary lesions. Peripheral aneurysms are usually associated with coronary artery aneurysms. Interstitial myocarditis, pericarditis, inflammation of the sinoatrial node and atrioventricular conduction system, endocarditis and valvulitis were also present.[53]

The similarities of the clinical and pathological findings of MCLS to those of infantile polyarteritis nodosa (IPN) have been well accepted by numerous investigators.[49,51,54–61] It is also clear that the clinical, pathologic, and histologic findings in IPN and MCLS are quite dissimilar to those of polyarteritis nodosa of the adult type.

Most of the investigators would agree with our opinion that Kawasaki disease and IPN are the same disease, and if they are not the same, they are indistinguishable. The first nationwide survey on MCLS in 1970 disclosed 10 death cases in Japan. A postmortem examination had been performed in four patients and IPN was the initial histopathological diagnosis in all. Dr. Kawasaki himself reported two cases of fatal MCLS as IPN in 1970. MCLS was considered to be a self-limiting benign disease at that time.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of Kawasaki disease is entirely clinical and no specific diagnostic test is available. The diagnostic guidelines of Kawasaki disease prepared by the Japan Kawasaki Disease Research Committee (Table 89–1) and the diagnostic criteria from Centers for Disease Control (CDC) for Kawasaki disease are useful for establishing the diagnosis in cases with typical clinical features. The CDC criteria for Kawasaki syndrome are as follows: 1) fever lasting 5 or more days associated with at least four of the following five features—bilateral conjunctival injection; one or more changes of the mucous membranes of the upper respiratory tract, including pharyngeal injection, dry, fissured lips, and "strawberry tongue," one or more changes of the extremities, including peripheral edema, periungual desquamation, and desquamation of hands and feet; rash, principally truncal; cervical lymphadenitis; and 2) the absence of another known disease process that could explain the findings.[62] But the situation differs in the atypical or mild case since no pathognomonic laboratory features have been established.[63,64]

The differential diagnosis of Kawasaki disease includes scarlet fever, Stevens-Johnson syndrome, juvenile rheumatoid arthritis, sepsis, and others. Kawasaki disease often has been misdiagnosed

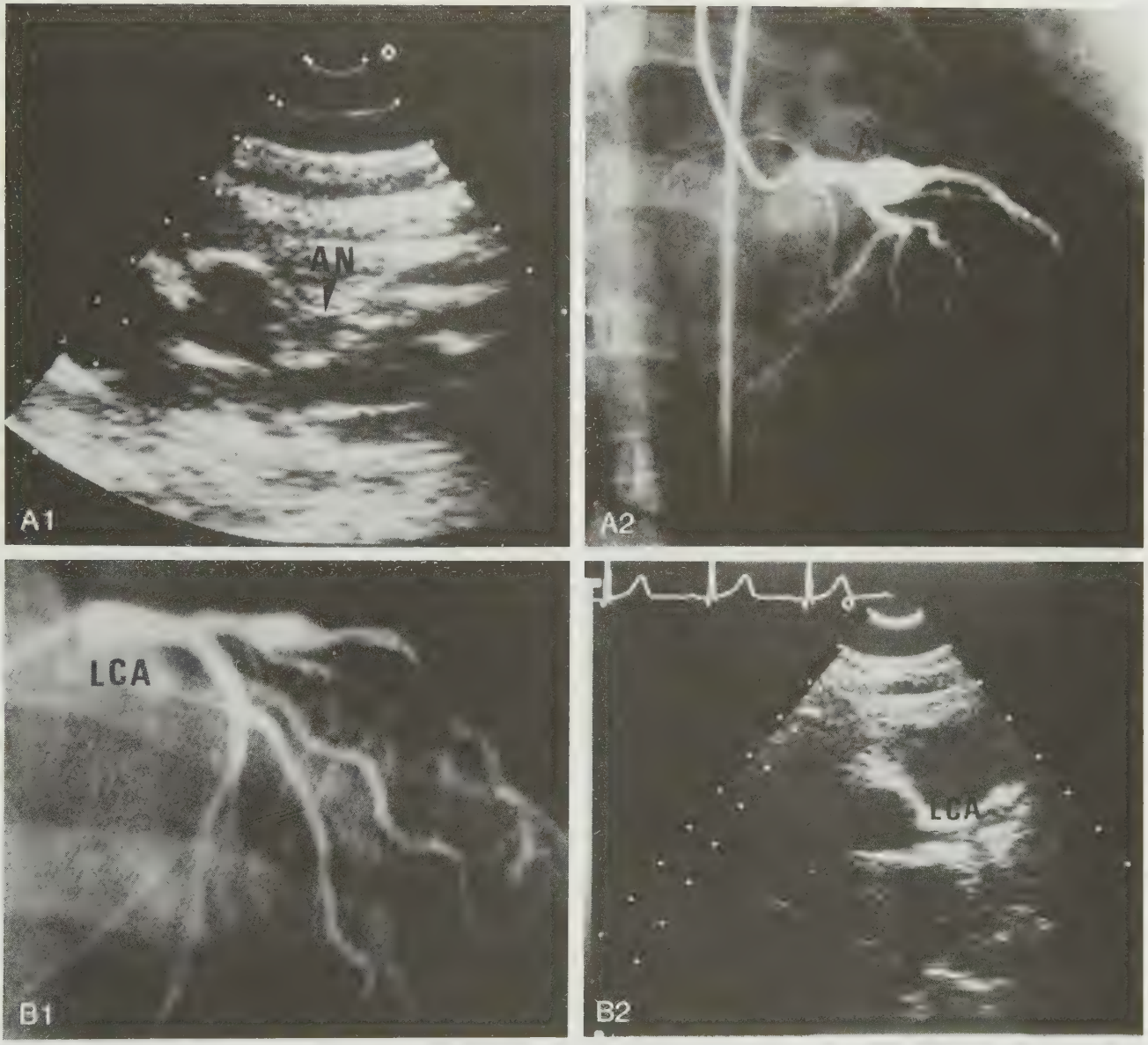

Fig. 89–8. Matching sets of two-dimensional echocardiograms and selective coronary angiograms from five patients. For each patient, the same view is shown for the echocardiogram and angiogram. The proximal part of the arteries are the sites of involvement in the majority of cases, but isolated peripheral abnormalities could also develop. Coronary artery findings can be classified into four categories, i.e., occlusion; stenosis, segmental and localized; aneurysm (AN), saccular and fusiform; and dilatation. AO = aorta, LCA = left coronary artery, RCA = right coronary artery.

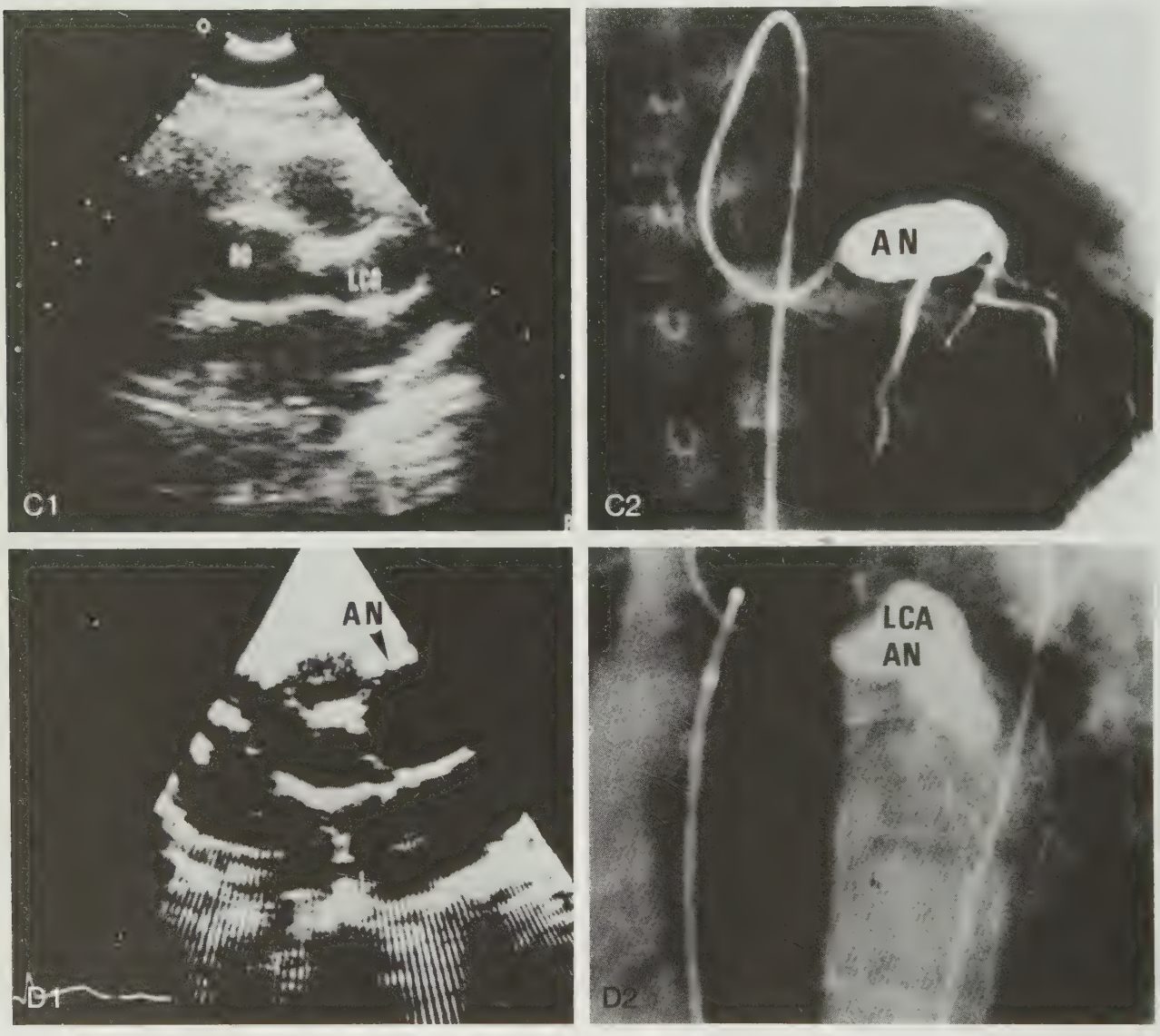

Fig. 89–8 *continued.*

Table 89–2. Etiological Agents of Kawasaki Disease So Far Proposed

Bacteria: Streptococcus, Streptococcus sanguis, Staphylococcus, Yersinia
Anaerobic propionibacterium
Fungi: Candida
Rickettsia or rickettsia-like bodies
Virus: EB virus, RS virus, Rotavirus, Herpesvirus, Retrovirus, Toxoplasma
Leptospira
Mite
Chemical substances: mercury, detergent, antibiotics

as scarlet fever or streptococcal infection because of the similarities of clinical manifestations such as fever, rash, strawberry tongue, cervical lymphadenopathy, and desquamation. But in scarlet fever, the rash is not polymorphous, conjunctival congestion is absent, desquamation is seen all over the body, and antibiotics are effective. Most importantly, scarlet fever is rarely seen in children under 3 years of age.

In earlier days many physicians diagnosed Kawasaki disease as Stevens-Johnson syndrome. Although a severe case of Stevens-Johnson syndrome with rash, purulent vesicles, and involvement of mucous membrane of various parts of the body is not difficult to diagnose, a milder form may be confusing. Acute-onset juvenile rheumatoid arthritis (JRA) is another important disease to be differentiated. In the early phase of the disease it is particularly difficult to distinguish the common symptoms such as fever, rash, and swelling of the joints of hands and feet. In JRA, the absence of conjunctival congestion, changes of lips, and desquamation in the convalescent stage are useful in establishing the diagnosis. To rule out septicemia is particularly important since adequate treatment with antibiotics is urgent.

Measles, rubella, and other viral exanthematous diseases require continued observation to differentiate them from Kawasaki disease; usually this is not difficult since the courses are different.

Children with Yersinia infection may meet the diagnostic criteria of Kawasaki disease.[29] Serum antibody titer and isolation of bacteria from the stool should establish the diagnosis. Other possibilities to be included are anaphylactoid purpura, staphylococcal scalded skin syndrome, leptospirosis, Rocky Mountain spotted fever[65] and other rickettsioses.[66,67]

ETIOLOGY

In spite of extensive research, the etiology of Kawasaki disease remains unknown. Several epidemics in the past, the high incidence among siblings, and geographic characteristics including clustering favor an infectious agent as the cause. But the preponderance of males and the high incidence among Japanese infants or those who have Japanese backgrounds are against an infectious etiology. Etiological agents of Kawasaki disease so far proposed are summarized in Table 89–2.

Among many bacteria, streptococcus is the one that has been most extensively investigated. Ueno and Matsumi[68] demonstrated elevation of cellular antistreptolysin O (ASO) and lymphocyte ASO during the acute stage. They proposed streptococcal exotoxin (SPE) as an agent but streptococci have not been isolated from the patients. Streptococcus sanguis, known as a causative agent of bacterial endocarditis, has been isolated from patients and their mothers, but its role as a causative agent in Kawasaki disease is not confirmed.

Yersinia pseudotuberculosis infection produces clinical symptoms similar to Kawasaki disease and it has been isolated from stool cultures in patients who were diagnosed clinically as Kawasaki disease according to the diagnostic criteria.[29] A significant titer change in agglutinating antibody was also confirmed in these patients. But that is not the case in all patients with Kawasaki

Fig. 89–8 ***continued.***

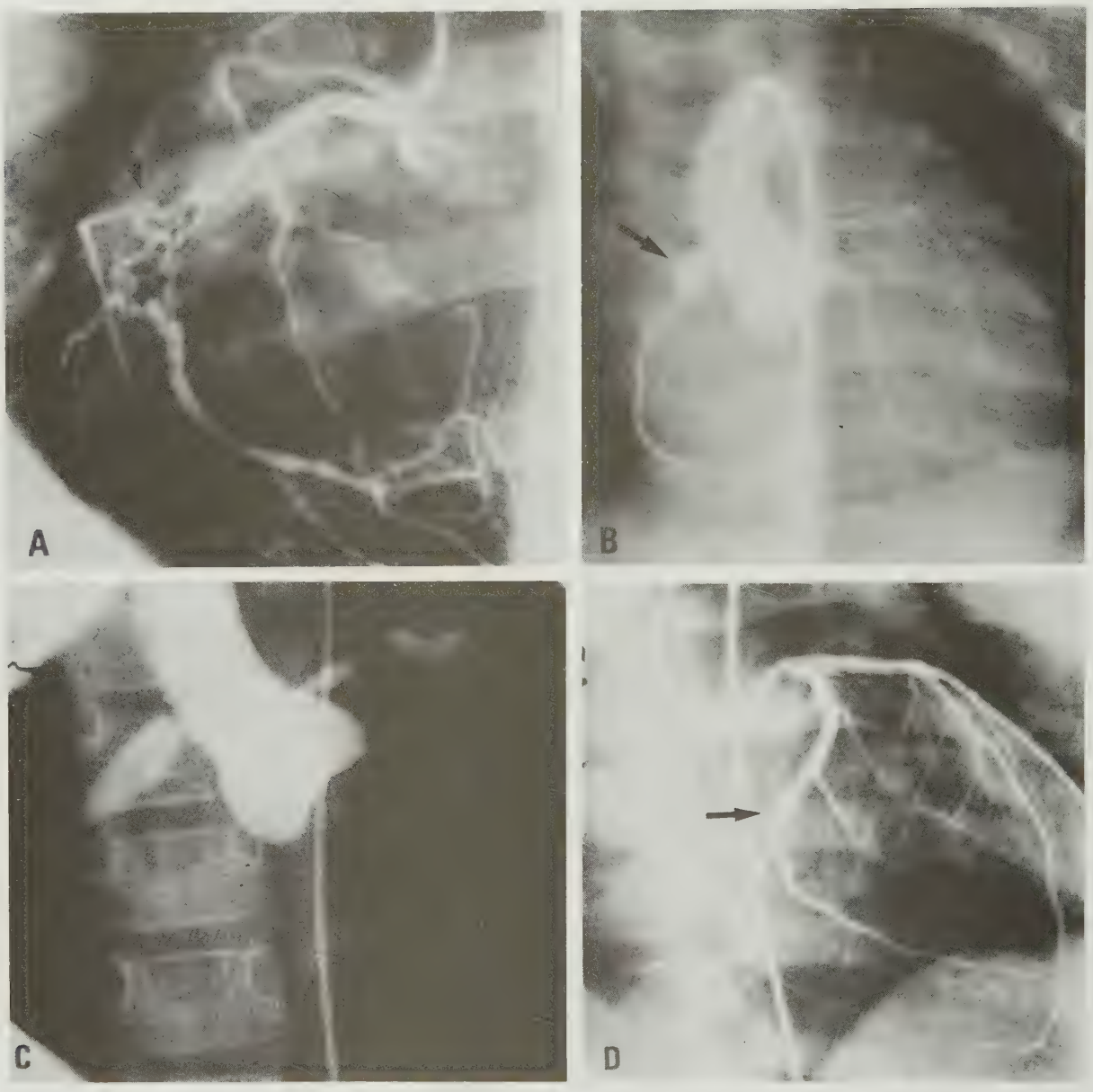

Fig. 89–9. (A) Selective right coronary angiography of an 8-year-old asymptomatic boy showing well developed collaterals and recanalization in the previously confirmed aneurysm. This patient had Kawasaki disease at 6 months of age. (B) Isolated saccular right coronary artery (RCA) aneurysm of a 9-month-old boy who had Kawasaki disease at 3 months of age. His fever persisted for more than 3 weeks. (C) Fusiform RCA aneurysm of a 5-year-old girl who had Kawasaki disease at 4 years, 2 months of age. Her clinical course was fair with fever lasting for 8 days. (D) Peripheral fusiform dilatation of the left circumflex coronary artery (LCX) of a 6-year-old boy who had Kawasaki disease at 1 year, 6 months of age.

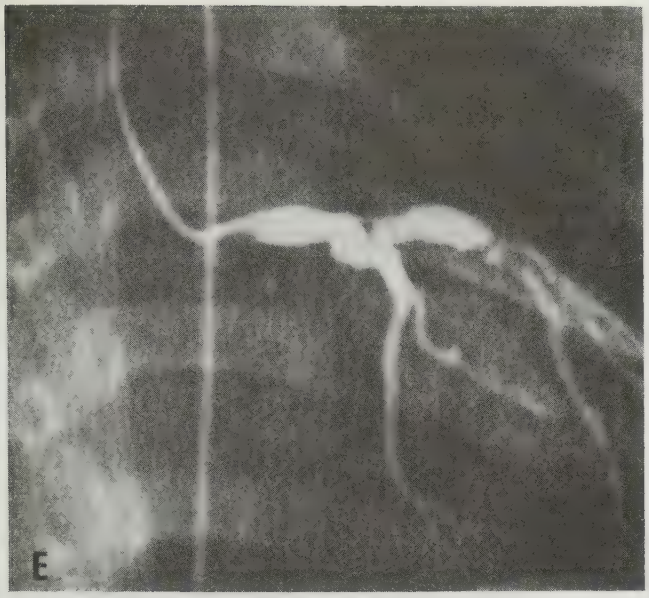

Fig. 89–9 *continued.* (E) Aneurysms with localized stenosis of a 3-year, 3-month-old boy who had Kawasaki disease at 11 months of age. He has been completely asymptomatic.

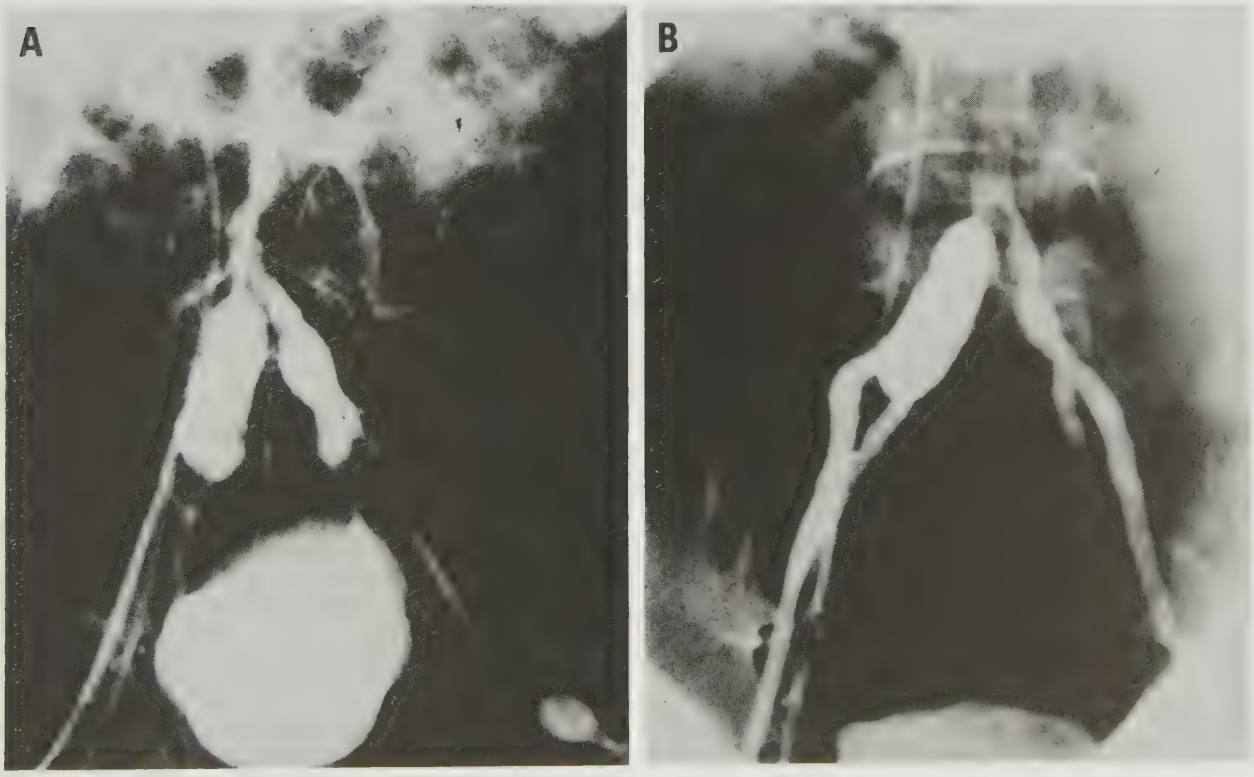

Fig. 89–10. Serial abdominal angiograms of the same patient as Figure 89–7. (A) At 3 months after onset of Kawasaki disease, there were multiple lesions involving abdominal aorta, renal, and bilateral iliac arteries. Both right and left femoral arteries were barely patent with isolated saccular aneurysm on the left. (B) Four years later, some degree of regression was confirmed and there was adequate flow through both femoral arteries.

disease. In Japan three children with Yersinia pseudotuberculosis infection who met the diagnostic criteria of Kawasaki disease were reported to have coronary aneurysms.

A variant strain of Propionibacterium acne,[69] staphylococcus, and salmonella[70] are also under consideration as causative agents, but no direct evidence has been demonstrated.

An abnormal immune response of the patient with Kawasaki disease to Epstein-Barr virus has been revealed.[71,72] According to Osato,[73] EB viral capsid antigen (VCA)-specific antibody responds positively in 93% of patients with MCLS within 3 months after the onset of acute stage, but titers are abnormally low. Rotavirus and common viruses such as adeno type 3 virus, herpes simplex virus, echo 11, HB antigen and most recently retrovirus[74] may play roles as causative agents, but again no single virus has been confirmed. Circulating immune complexes containing mite antigen have been demonstrated in the serum of patients[75–77] and intradermal reaction by mite antigen is positive in many of the cases. Certain mites were reported to be commonly found in the dust from the houses of patients, but case-control studies showed no difference in the number of mites.[78–80]

Although mercury poisoning (acrodynia) once was thought to be a pathogen of Kawasaki disease because of the similarities of the symptoms such as swelling, pink coloration and desquamation of the hands and feet,[81,82] patients with Kawasaki disease have had normal mercury levels and contents in hair and urine.[83,84] Other chemical substances so far proposed in relation to Kawasaki disease are antibiotics (tetracycline), detergents, and rug shampoo,[85] however, no associations have been confirmed. Thus the etiology of Kawasaki disease remains unknown.

COMPLICATIONS

Cardiovascular

Although it took several years after the original report by Dr. Kawasaki,[1] it has become quite obvious that the most serious complications of Kawasaki disease are cardiovascular. Cardiovascular involvement usually appears in the second week of illness when gallop rhythm, distant heart sounds, electrocardiographic changes, and cardiomegaly on chest roentgenography are often observed (Fig. 89–11). These findings progress in the second and third weeks of illness and except for severe cases, improve at the end of the fourth week.

Cardiovascular complications include arteritis and aneurysm formation of the coronary arteries, myocarditis, pericarditis, pericardial effusion, arrhythmias, and valvular disease.[8,10,36,64,86–94] Myocarditis, pericardial effusion, and valvulitis usually improve after about 1 month of illness in most of the cases; however, vasculitis of the coronary arteries follows a unique course. Dilatation of the coronary arteries due to vasculitis is recognized in about 50% of the patients beginning at 7 to 8 days of illness. The left coronary artery is involved in more patients than was the right, and the proximal parts of the left or right coronary arteries are most frequently involved. More distal parts of the coronary arteries are occasionally involved, making detection difficult by echocardiography. The dilatations or aneurysms remain even after the acute phase in 10 to 20% of patients. According to Kato,[94] of 713 patients who underwent aortography and/or coronary angiography at 1 to 3 months after onset of the disease, 161 (23%) had coronary aneurysms. Of 128 patients who were documented to have coronary aneurysms during the acute phase, angiographic findings became normal in 73 (57%), suggesting regression of the aneurysms in 1 to 2 years after the acute illness. In the remaining 55 cases, coronary artery lesions such as aneurysms, stenosis, obstruction, and irregular arterial walls persisted. Kamiya and Suzuki[95] have accumulated angiographic data on 1000 patients who were studied 2 years after the onset of the disease; 246 cases (25%) had coronary artery lesions; 154 of the 246 (63%) had aneurysms or dilatation, 60 (24%) had localized stenosis, 14 (6%) had segmental stenosis, and 18 (7%) had occlusion of a coronary artery. A giant coronary aneurysm with a diameter of 8 mm or more and saccular, sausage-shaped, or multiple aneurysms are considered to be important risk factors in the progression to stenosis or occlusion. Ischemic heart disease may develop in less than 3% of patients. Peripheral aneurysms in arteries other than the coronaries were usually found in patients with severe clinical symptoms of the acute phase and were usually accompanied by coronary lesions. According to Kato,[96] of 513 patients in his series 13 (2.5%) had peripheral aneurysms, axillary in 12 patients, iliac in 11, renal in 4, and internal thoracic artery in 3. Kamiya and Suzuki[95] also identified aneurysms and/or localized stenosis of the arteries other than coronary in 10 of 1000 cases (1%).

Diagnosis of coronary artery lesions in Kawasaki disease by two-dimensional echocardiography has been well established and its diagnostic sensitivity is reported to be 80 to 90%[39–46] (see Fig. 89–8). Use of a high-frequency transducer of 5 mHz is recommended as the patients are usually infants and younger children. Stenotic lesions may be detectable by echocardiography but in most of the cases are difficult to demonstrate. Prediction of the development of coronary lesions has been investigated. According to Asai et al.[97] who have proposed a ''score table'' for determining the indication for angiography, those patients with the following clinical symptoms and signs are likely to develop coronary artery involvement:

1. male infant less than 1 year of age
2. prolonged fever for more than 16 days or recurrent fever
3. peripheral white blood cell count greater than 30,000 mm
4. erythrocyte sedimentation rate (ESR) greater than 101 mm/hr
5. elevated ESR or C-reactive protein titer for more than 30 days of illness
6. reappearance of elevated ESR or C-reactive protein titer
7. electrocardiographic abnormality (abnormal Q wave in leads II, III, aVf)
8. symptoms of myocardial infarction

Koren[98] found from the Asai et al. data on 163 patients with Kawasaki disease that fever lasting for more than 14 days can be used as a single criterion in predicting risk of coronary disease, that coronary artery involvement occurred with equal frequency in boys and girls, and that there was no significantly greater incidence of coronary artery involvement in infants younger than 1 year of age.

For the early prediction of coronary involvement while the patient is still febrile, Burns et al.[99] have suggested elevated plasma β-thromboglobulin as a sensitive means of differentiating patients with coronary aneurysms from those with normal coronary arteries. Other investigators[26,100] have pointed out hypoalbuminemia as a predicting factor of coronary involvement. Regardless, frequent

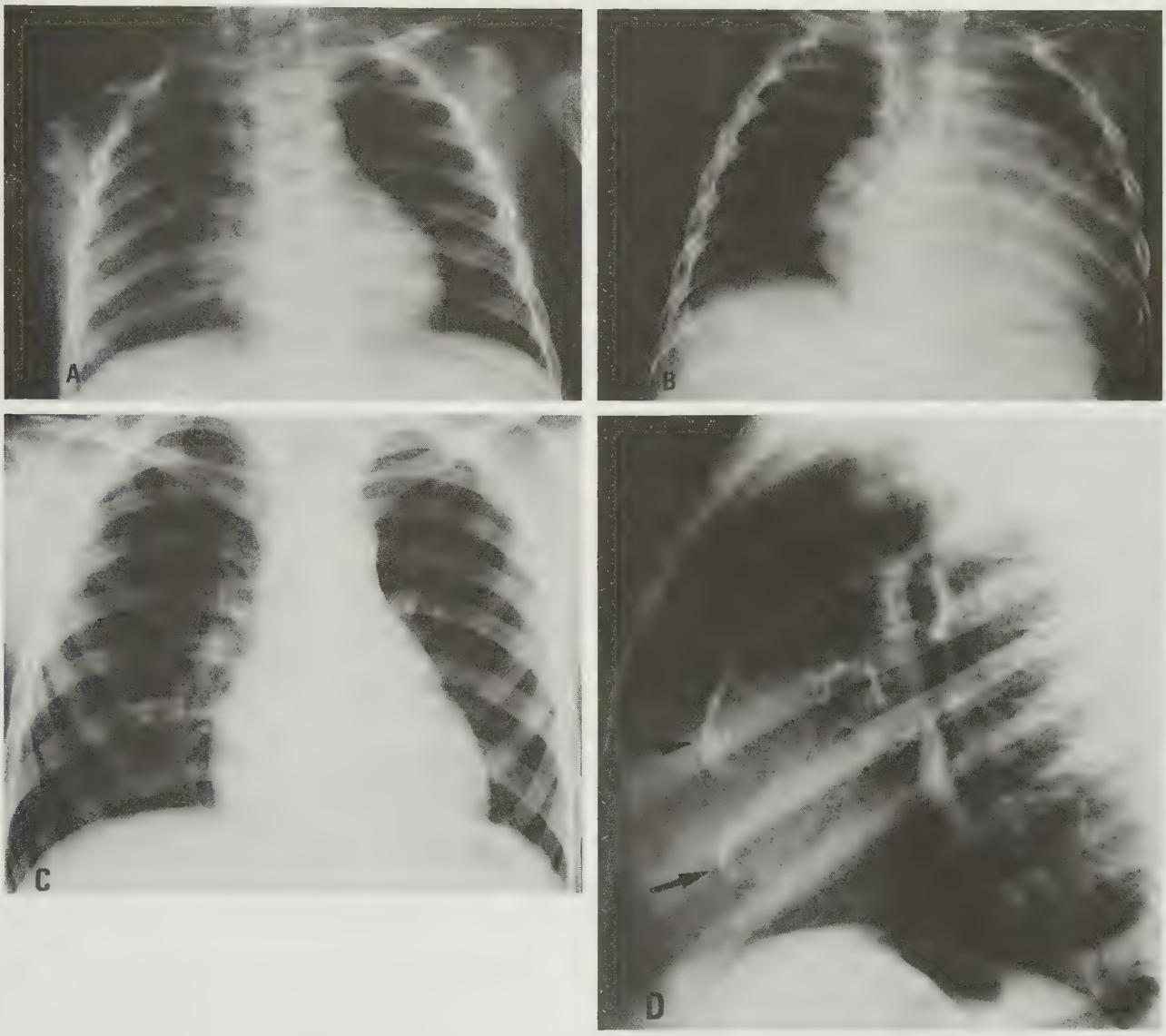

Fig. 89–11. Serial chest roentgenographs of the same patient as in Figure 89–7. Two PA views were taken in the acute phase. At the onset of fever (A), there were no abnormal findings. However, 3 weeks later he developed marked cardiomegaly (B). Now, at 7 years of age, on both PA (C) and lateral (D) views, calcified multiple giant coronary artery aneurysms are recognized. His myocardial scintigram shows no remarkable changes.

and serial two-dimensional echocardiography is indispensable in evaluating cardiovascular lesions.

The role of selective coronary angiography in evaluation and management of patients with Kawasaki disease is controversial. Although the proximal part of the left or right coronary artery where lesions are detected by echocardiography is more frequently involved, aneurysm or dilatation can develop in the more distal part of the coronary arteries and normal echocardiographic appearance of the proximal right or left coronary arteries may not rule out the involvement of the more distal part of the coronary arteries. In addition, the majority of cases with coronary artery lesions have normal electrocardiographic, chest roentgenographic, and also auscultatory findings. It has been generally considered reasonable to perform coronary angiography in patients known to have coronary lesions. Kamiya and Suzuki[95] from their experiences of selective coronary angiography on 1000 cases recommended repeating the study 1 year later on patients in whom coronary artery involvement was detected at the first study. Of 190 cases restudied after 1 year, in 29% aggravation of the stenotic lesion was recognized, and in 61% aneurysms decreased in size. There were no serious complications of coronary angiography.

Pericarditis, usually with a small amount of pericardial effusion, occurs in about 30% of patients in the first to second week of illness.[101] Rarely it progresses to cardiac tamponade and pericardiocentesis may be necessary. Usually no specific treatment is needed.

Mitral regurgitation due to valvulitis or ischemia of the papillary muscle is observed in about 1% of patients with Kawasaki disease in the acute phase.[53,102] Usually it is mild and disappears, but in rare cases it causes congestive heart failure and requires digitalis, diuretics, and vasodilators.[103] Infrequently, aortic or pulmonary regurgitation develops due to valvulitis.[101]

Myocardial infarction due to thromboembolic occlusion of aneurysms or progression of the stenotic lesions accounts for the majority of the causes of death due to Kawasaki disease.[18] Analysis of 104 deaths in Japan revealed that more than half of the patients (60 cases, 57%) died of acute myocardial infarction while 7 patients (9%) died of congestive heart failure after myocardial infarction. Analysis of 195 cases complicated with myocardial infarction collected in Japan revealed that attacks of infarction developed within 1 year of onset in 142 patients (73%), more frequently within 3 months in 77 cases (40%); 43 patients (22%) died from the first attack and 26 of 43 (61%) had sudden death (death within 24 hours after the attack). Asymptomatic myocardial infarction was recognized in 73 patients (37%); chest pain is more frequently observed in children over 4 years of age (Figs. 89–12 and 89–13).

Other Complications

Complications involving liver and biliary tract are classified into three categories:

1. primary liver dysfunction due to Kawasaki disease itself,
2. hydropic gallbladder or acute cholecystitis,
3. secondary liver dysfunction induced by drugs.

Primary liver dysfunction characterized by elevated transaminases but not bilirubin in the first week of illness has been recognized in 17 to 26% of patients. At this point patients usually have not received any specific drugs, including aspirin. The development of hydropic gallbladder has been attributed to edematous change of the common bile duct due to vasculitis of the bile duct system

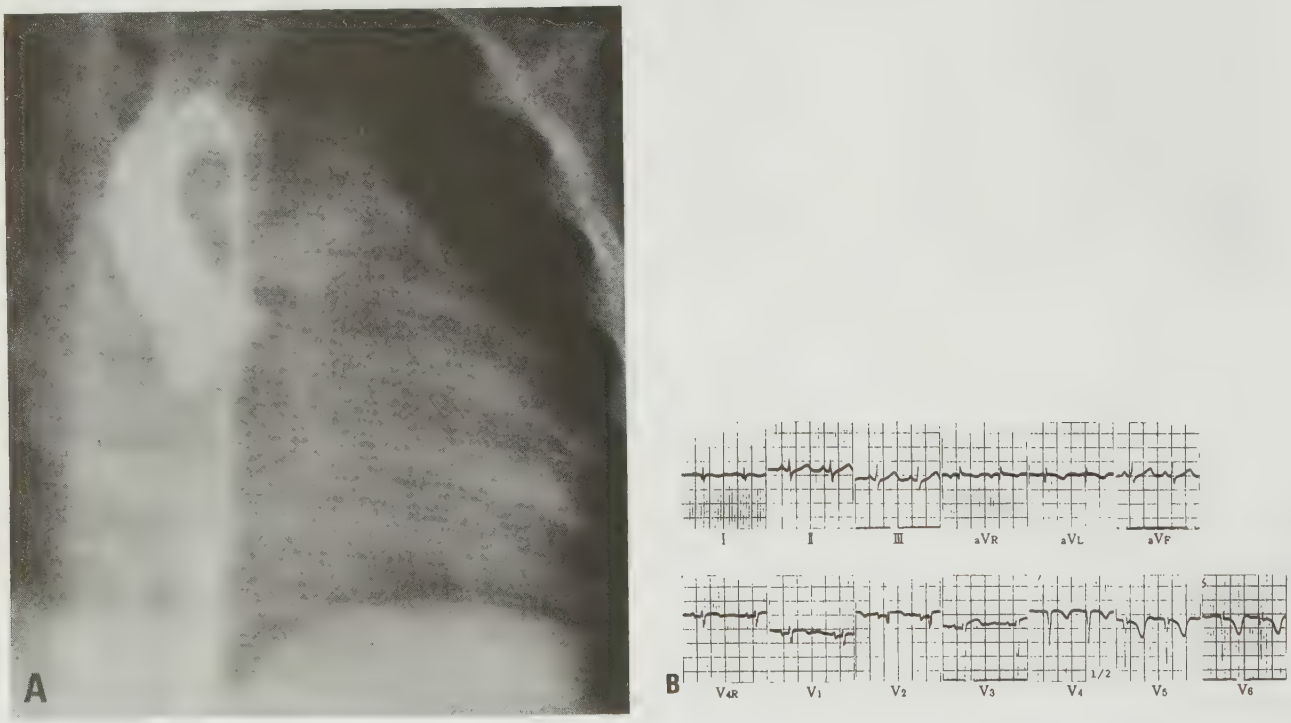

Fig. 89–12. Aortic root angiogram (A) and an electrocardiogram (ECG) obtained from a 2-years, 1-month-old patient, (B) 12 months after the onset of Kawasaki disease. Bilateral coronary artery aneurysms on angiogram and evidence of anterolateral myocardial infarction on ECG are recognized. Physical examination revealed mitral regurgitation of moderate degree.

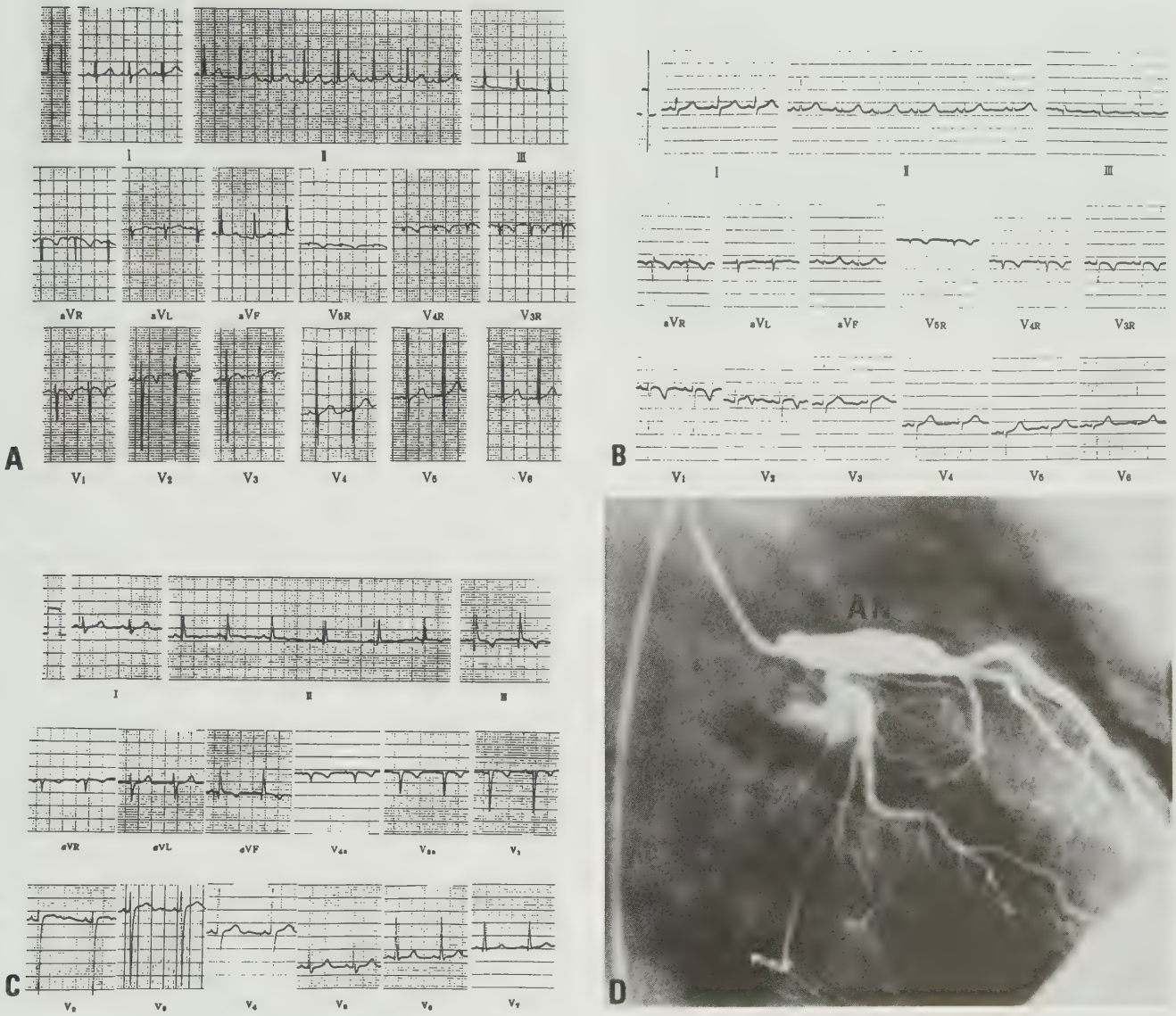

Fig. 89–13. Serial electrocardiograms of an 8-year-old girl who had Kawasaki disease at 2 years of age. At 7 years of age, she developed myocardial infarction but the symptoms were fairly mild, with abdominal pain and vomiting several times, which improved within a few hours. Compared to the tracing at 2 years, 10 months of age (A) and also at 4 years, 9 months of age (B), at 8 years ST-T changes in leads II, III, aVf, and q wave in leads III and aVf are obvious (C). D. Followup angiograms showed complete obstruction of the right coronary artery (RCA) at the orifice. There was late filling of RCA through collaterals from the left coronary artery (LCA). Ejection fraction by cineangiography was also abnormally low with 37%.

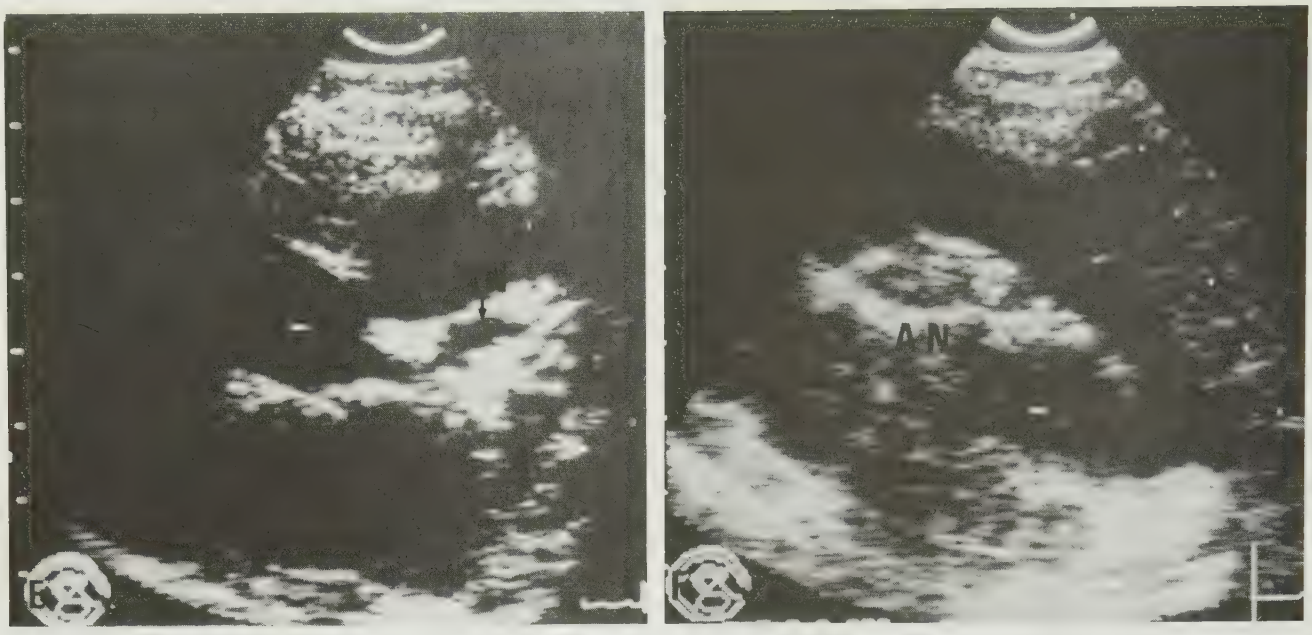

Fig. 89–13 *continued.* Two-dimensional echocardiograms showed aneurysmal change of LCA with dense echoes around the aneurysms indicating thickened arterial wall (E) and probable thrombi in RCA aneurysm (F).

including the gallbladder. In typical cases, a hydropic gallbladder is observed by ultrasonographic examination around 7 days of illness.[30–33] Laboratory examination reveals the pattern of obstruction of the biliary tract; elevated transaminases and bilirubin, elevated serum levels of total cholesterol, leucineaminopeptidase (LAP); and γ-glutamyltranspeptidase.

Patients with a hydropic gallbladder usually complain of abdominal pain or tenderness in the right upper quadrant, occasionally with vomiting and/or diarrhea. Hydropic gallbladder has been recognized in about 10% of patients with Kawasaki disease, more commonly in males.[8] About half of the cases have been seen in children over 5 years of age. Patients usually improve from this condition within 1 to 2 weeks, but rarely develop serious complications.[104,105] Liver dysfunction induced by aspirin has been well recognized.[106] Serum transaminases begin to elevate after 5 days to 2 months of administration but normalize within 1 to 2 weeks after cessation of aspirin.

Otitis media and aseptic meningitis are conditions commonly seen during the course of the illness. Other complications include moyamoya disease, Perthes' disease, ileus, nephritis and nephrosis, iritis, protein-losing enteropathy, pleural effusions, and urethritis; but all these conditions have been uncommon.

TREATMENT

Before 1977, Japanese physicians used mainly corticosteroids (prednisolone 2–4 mg per kilogram per day) since they seemed to be effective for fever and other clinical symptoms. Antibiotics were also given simultaneously. But a study on the effect of treatment on coronary artery involvement by Kato[107] showed that coronary angiography 1 to 2 months after the onset of disease demonstrated significantly increased incidence of coronary aneurysms in patients treated with steroids compared to those patients treated with antibiotics alone or aspirin. Since then treatment with corticosteroids has been abandoned in most of the centers taking care of large numbers of children with Kawasaki disease.[108] Japanese investigators have compared aspirin, flurbiprofen, and prednisolone plus dipyridamole in a total of 306 hospitalized patients with Kawasaki disease.[109] Coronary lesions were recognized at 1 month of illness in 22% of patients treated with aspirin, 39% with flurbiprofen, and 27% with prednisolone and dipyridamole. At 1 year after the acute illness, coronary artery abnormalities were observed in only 1% of cases treated with aspirin, but in 12% of cases with flurbiprofen and in 9% with prednisolone and dipyridamole. Aspirin is the most commonly used drug for Kawasaki disease at the present time. A recent survey in Japan revealed that almost 90% of patients with Kawasaki disease have been treated with aspirin.

Cases treated with a high dose of intravenous gammaglobulin have been increasing in both Japan and the United States. According to a nationwide survey in Japan, gammaglobulin was administered to 39% of patients in 1986 while to only 3% in 1982. Furusho and his colleagues[110,111] have evaluated immunoglobulin treatment for Kawasaki disease. In 6 of 40 cases (15%) treated with aspirin plus intravenous gammaglobulin (more than 1000 mg/kg), coronary artery lesions were detected by two-dimensional echocardiography within 29 days of illness, compared to 19 of 45 cases (42%) treated with aspirin alone.

The multicenter study by Newburger et al.[112] concluded that high-dose intravenous gammaglobulin (400 mg per kg of body weight per day for 4 consecutive days plus aspirin 100 mg per kg per day) is safe and effective. But still in 6 of 75 patients (8%) at 2 weeks and in 3 of 79 (4%) at 7 weeks after treatment with the above protocol, coronary artery abnormalities were recognized.

Further investigation is necessary to determine the minimal effective dose, frequency, and duration of treatment with gammaglobulin. Most importantly, long-term evaluation of the patients who had received high-dose intravenous gammaglobulin is needed. The mechanism by which high-dose intravenous gammaglobulin reduces the development of coronary artery lesions is

speculative. According to Leung,[113–115] in the acute phase of Kawasaki disease a decrease in suppressor T-cell activity for immunoglobulin production occurs. This can be normalized by a course of intravenous gammaglobulin for 4 days.

Recommended Treatment

Acute Phase (in Hospital)

Aspirin should be given once the clinical diagnosis of Kawasaki disease is suspected. Most Japanese pediatricians use a daily dose of 30 to 50 mg per kg of body weight divided in 3 doses. In the United States, however, an initial dose of 80 to 150 mg per kg per day has been recommended for 2 weeks or until the fever disappears.[116]

A controlled prospective study is needed to decide whether the use of high-dose aspirin is necessary or not. Monitoring of the blood salicylate level is recommended to avoid salicylate toxicity since during the acute phase, there seems to be malabsorption of aspirin. In Japan, low-dose aspirin has been effective in decreasing the incidence of coronary artery abnormalities. Most Japanese physicians continue daily aspirin (30 mg per kg) until the end of the second month, regardless of coronary artery involvement. In the United States, however, aspirin is reduced to 30 mg per kilogram per day once the fever disappears, and usually is continued until the end of the fourth week. Hospitalization and bedrest are the general rules for children in the acute phase. Therefore, our patients stay in the hospital at least for 3 to 4 weeks after the onset. As to the use of high-dose intravenous gammaglobulin, we think that severely ill patients are candidates at the present time, although in the United States, Newburger et al.[112] have recommended that all children with Kawasaki disease receive this form of therapy.

Most infants and children at this stage are markedly irritable and have a poor appetite. Intravenous fluid therapy is usually necessary. Once the fever disappears, patients feel comfortable and their appetite improves. Even so, the second and the third week of illness are the most critical period since patients are at the highest risk of coronary embolism, myocardial infarction, and death. Sudden onset of shock, pallor, vomiting, severe crying, dyspnea, chest pain, and convulsion were the documented symptoms at the time of death in 104 cases in Japan. When symptoms of myocardial infarction are noted, oxygen, vasodilators (nitroprusside, nitroglycerine), and catecholamines (dopamine, dobutamine) may be required. Anticoagulation with heparin and urokinase is advised, and if necessary, direct infusion of urokinase into the coronary arteries may be considered. Defibrillation, cardiac pacing, and/or administration of antiarrhythmic drugs such as lidocaine (Xylocaine) may be indicated.

Otherwise, in the hospital, except for daily checks of physical findings especially related to the cardiovascular system, we recommend weekly (or preferably twice weekly) determination of: CBC, platelet count, C-reactive protein titer, ESR, serum transaminases, serum protein, A/G ratio, urinalysis, BUN, creatinine, electrocardiogram, chest roentgenogram, and two-dimensional echocardiogram. If coronary or peripheral artery abnormalities are detected in the acute stage, dipyridamole (3 to 5 mg per kg per day) may be added to the usual dose of aspirin.

Patients are discharged when the clinical manifestations disappear, the hematological and serological findings improve, and the electrocardiographic and chest roentgenographic findings normalize. Patients may be discharged with coronary artery abnormalities unless there is evidence of embolism or infarction.

Subchronic Phase

We discontinue aspirin after 2 months in patients without coronary lesions as confirmed by two-dimensional echocardiography and/or cineangiography. Essentially no restriction of activities is necessary. Vaccination may be resumed after 2 months of illness. Although patients without sequelae are extremely unlikely to develop any signs or symptoms of cardiovascular abnormalities, we recommend yearly followup since any patient who has experienced Kawasaki disease in infancy may have a predisposition to development of atherosclerosis of coronary arteries in the early adult life. For those patients with coronary lesions after 2 full months of illness, we recommend continuation of antithrombotic therapy. A dose of 5 to 10 mg per kg of aspirin is administered once a day. In addition, dipyridamole (5 mg per kg per day in three doses) is often used. Since a single antithrombotic agent may be insufficient, combination therapy of aspirin and other drugs is recommended.[101,117,118]

Evaluations by electrocardiogram, chest roentgenogram, two-dimensional echocardiogram, and exercise test on a treadmill or bicycle once every 2 to 3 months should be planned. Blood samples should also be drawn to check for side effects of aspirin and other drugs.

Angiographic evaluation of coronary arteries is necessary in patients with cardiovascular sequelae although recent advances in echocardiography have enabled physicians to follow these patients noninvasively. We recommend performing selective coronary angiography on patients who have the following features:

1. Severe cardiovascular sequelae such as myocardial infarction, angina pectoris, valvular disease of moderate degree or more, and serious arrhythmias.
2. Persisting coronary aneurysms or dilatation by echocardiography beyond 6 months after the onset of the acute stage, but without any symptoms. Obstructive lesions should be ruled out in these patients.
3. When followup electrocardiography and/or exercise stress testing suggests myocardial ischemia, after echocardiography showed coronary aneurysms or dilatation during the acute stage, which regressed afterwards.

Symptoms such as chest pain or severe arrhythmias are signs that indicate a need for immediate angiographic evaluation. In those patients with cardiovascular sequelae documented by echocardiography but without any symptoms, coronary angiography may be scheduled between 6 to 12 months after the onset. Evaluation only by echocardiography may be misleading. Often, especially in patients with severe cardiovascular sequelae, angiographic evaluation should be repeated at certain intervals.

As described before, regression of coronary lesions is expected, especially in patients with mild fusiform dilatation and a diameter less than 8 mm. Generally, no restriction of daily activities is necessary in patients with coronary abnormalities but without obstructive lesions; however, hard exercise such as short dash, marathon, and competitive sports should be individualized. Those patients with obstructive lesions may be asymptomatic or may

suffer from angina pectoris, myocardial infarction, and even sudden death. Antithrombotic therapy is absolutely indicated but dipyridamole may not be indicated in cases with severe obstructive lesions of the coronary arteries since it may induce coronary steal. Patients with angina pectoris may be treated with calcium antagonists, beta-blockers, and nitrites or may require coronary bypass surgery. More recently, percutaneous transluminal coronary angioplasty has become a popular treatment for adults with coronary disease; it is possible this may be applied to children. Patients should be followed closely with electrocardiography, two-dimensional echocardiography, exercise stress test, thallium myocardial scintigraphy, and coronary angiography.

The followup interval depends on the condition of the individual patient. Some require weekly check-up, some monthly or quarterly. Daily activities of the patient with obstructive lesions should be determined according to the clinical symptoms and the result of the various tests mentioned above.

Coronary artery bypass surgery is considered in patients with the following features.[101,118–123]

1. Severe occlusion of the left main coronary artery or of more than one vessel,
2. severe occlusion in the proximal portion of the left anterior descending artery and poor collateral circulation.

An autologous great saphenous vein or internal mammary artery may be used for grafting. In view of the longterm patency of the grafts, the use of internal mammary artery may be preferred.[124] According to the experience on 55 surgically treated children collected in Japan, 31 patients improved but 5 patients died after surgery.[125,126]

For those patients with a history of Kawasaki disease, we recommend followup by a pediatric cardiologist. Examination should include precise history and physical examination, chest roentgenography (both anteroposterior and lateral views), exercise electrocardiogram, and two-dimensional echocardiography (Figs. 89–8, 89–11, 89–13, and 89–14). Some patients may need to be studied by angiography. Some may have a murmur of mitral regurgitation, calcification of the coronary aneurysms, and/or ECG abnormalities such as deep Q waves and ST-T changes.

FUTURE

The fatality rate of Kawasaki disease in Japan averages 0.5%, although it was reported initially to be 1.7%.[127] Therefore, in almost 99% of patients, at least the short-term prognosis is quite promising.

Problems arise about the possible long-term effects of vasculitis and aneurysm formation of the coronary arteries.[128] Regression of the coronary artery lesions of Kawasaki disease are well known but it is doubtful whether the coronary arteries become completely normal from the pathological point of view. Tanaka[49] reported residual coronary artery lesions in a child who was supposed to have had no coronary abnormalities in the acute phase. Those patients without documented sequelae have to be followed.[129,130]

Concerning the treatment and management, the main problems are

1. there has been no specific treatment regimen,
2. prediction in early active phase of the disease of eventual coronary artery lesions is extremely difficult, and
3. the question remains unanswered as to whether rapid improvement of the clinical manifestations with the use of high-dose intravenous gammaglobulin also implies "less chance" to develop coronary artery abnormalities.

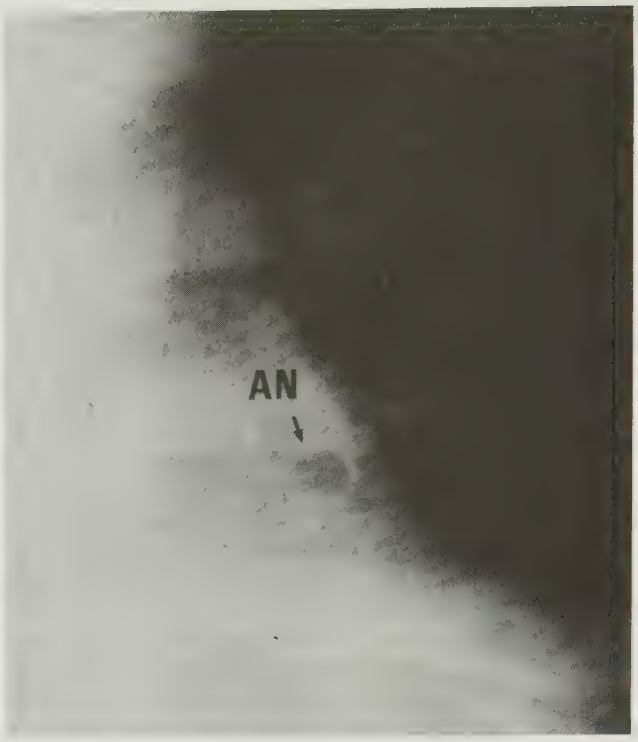

Fig. 89–14. PA view of a calcified left coronary artery aneurysm of a boy who had Kawasaki disease at 1 month of age. He had developed mitral regurgitation in the acute phase.

Modern technology represented by digital subtraction angiography (DSA), nuclear magnetic resonance imaging (NMR), and computed tomography may take place of selective coronary angiography and enable us to evaluate these patients noninvasively and safely.

Until further data become available, all individuals with a history of Kawasaki disease should be followed at certain intervals regardless of cardiovascular abnormalities.

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CHAPTER 90

Infective Endocarditis

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Infective endocarditis (IE) refers to a condition in which an organism or organisms infect the endocardium, the valves, or related structures. Previous injury to these structures by surgery, trauma, or disease usually has occurred. The infecting organism may be bacterial, fungal, chlamydial, rickettsial, or viral. In the first half of the twentieth century, a large percentage of patients with IE had prior rheumatic heart disease.[1] More recently, the majority of children with IE have complex congenital heart defects. Previous classifications divided cases between acute bacterial endocarditis (rapid, fulminant course with death occurring within 6 weeks) and subacute bacterial endocarditis (slow, indolent course, usually of several months' duration). The acute form usually was caused by Staphylococcus aureus, Streptococcus pyogenes, or Strep. pneumoniae, while the subacute form most commonly involved the viridans Streptococci. However, newer classification is based on microbiologic etiology rather than description, and the general term *infective endocarditis* is the more widely accepted term today.

EPIDEMIOLOGY

There is a wide disparity reported in the literature in the incidence of infective endocarditis in children. Most large series are retrospective and do not report the total number of admissions to that institution during the study period. During the decade 1952–1962, Zakrzewski and Keith[2] reported an incidence of infective endocarditis of 1 in 4500 pediatric admissions to the Hospital for Sick Children in Toronto. Johnson et al.[3] reported that 1 in 1800 admissions to Boston Children's Hospital during 1963–1972 were endocarditis, but that during 1933–1963 the incidence was only 1 in 4500. Finally, during 1972–1982, 1 in 1280 pediatric admissions to Case Western Reserve–Rainbow Babies Hospital was for endocarditis.[4]

The mean age of children with endocarditis is rising, almost certainly due to increased longevity following corrective or palliative surgery. Between 1930 and 1950 the average age was approximately 5 years,[5] but between 1960 and 1980 this increased to 8.5 to 13 years.[3,5,6] However, a large retrospective study comparing operated and unoperated children with congestive heart disease (CHD) who developed IE demonstrated no difference in the mean age of these groups of patients.[7]

A rapid rise has occurred in the incidence of IE in neonates without congenital heart defects. This increase seems to be associated with advances in life support in this population and the frequent use of indwelling catheters for nutritional and/or pharmacologic support.[8–12]

Virtually any congenital defect, including secundum atrial septal defect,[13–15] may predispose a child to the development of infective endocarditis. For example, Shah et al.[16] determined that the lifetime risk of developing IE in a patient with an unrepaired, simple ventricular septal defect (VSD) was 12 to 13%, while Steeg et al.[17] found that the risk was 3.2% over the first decade of life. In a large cooperative study on the natural history of aortic stenosis, pulmonic stenosis, and VSD, Gersony and Hayes[18] reported a risk of 9.7% of patients with unoperated VSD developing IE by age 30 years. However, if the patient underwent surgical repair, the incidence of IE was much lower. In contrast, the risk for patients with aortic stenosis (AS) (1.4%) was slightly increased after sur-

gical intervention; while patients with pulmonic stenosis had a 0.9% risk of developing IE.

In another study of 266 children, tetralogy of Fallot accounted for the largest percentage of patients with CHD who developed IE.[19] Similar findings are reported in other series from South Africa,[20] New York City,[21] and France.[22] Ventricular septal defect was the second most common lesion, accounting for 16% of the group, followed by AS (8%), patent ductus arteriosus (7%), and transposition of the great vessels (4%). However, other studies report that VSD[23,24] or aortic valve disease[25] (bicuspid aortic valve, aortic stenosis) were more common predisposing lesions. The most common lesions found in patients with CHD who developed endocarditis after surgery were tetralogy of Fallot (repaired with a systemic-pulmonary shunt) and transposition of the great vessels with pulmonary stenosis (repaired with a systemic-pulmonary shunt).[26] Several other patients had complex cyanotic CHD with shunts. Seventy percent of this group developed IE late (1 to >5 years) after their surgery. Similarly, in patients requiring prosthetic valves, 79% developed their infections more than 3 months after surgery. Predisposing events inducing a bacteremic state were identified in about one third of these cases. Details concerning the unoperated patients with underlying heart disease in this study are not well described but it appears the majority had either congenital valve deformities or valve disease secondary to rheumatic fever.

A smaller series from Yale–New Haven Hospitals found a higher incidence of IE in patients with CHD who had not undergone surgery than in those who had to be operated on.[6] Acyanotic lesions were more common in the unoperated group, while cyanotic lesions predominated in the postoperative group. Dacron patches and Gore-Tex grafts were more common sites of infection than prosthetic valves.

It appears that patients with "complete correction" of tetralogy of Fallot have a very low incidence of endocarditis compared with those patients who remain palliated. In a large series of 106 patients operated on from 1954–1960 and followed for a mean of 23.7 years, only one patient (1%) developed IE and no residual defects were noted in that patient at postoperative catheterization.[27]

Tricuspid atresia with diminished pulmonary artery flow is commonly palliated with a shunt procedure, usually a Waterston or classic Blalock–Taussig shunt. Patients receiving a classic Blalock–Taussig shunt may have an incidence of IE approaching 25%,[28] although a more recent series from Boston notes an incidence of 17%.[29]

Infective endocarditis associated with prosthetic materials, especially valves and valved conduits, is likely to increase in the future.[6,30] Prosthetic valve endocarditis (PVE) has been categorized as early (within 3 months of implant) or late onset. The incidence of infection ranges from less than 1% to 10% following implantation,[31–38] with a lower incidence being noted in the more recent series. Neither the type of valve nor the site of implant significantly affects the incidence of PVE.[38] Staphylococcus sp. predominate in early PVE, while Streptococcus sp. are the most common cause of infection in late-onset disease.[32–38] This pattern is probably a reflection of intraoperative contamination. The overall incidence of early PVE has been greatly reduced since the standard administration of perioperative antibiotics was instituted.

PATHOPHYSIOLOGY

Experimental animal models as well as clinical and autopsy investigations have shown that a series of events creates an environment suitable for the establishment of IE. Hemodynamic factors that predispose to turbulent blood flow and subsequent endothelial damage have been long studied. Lepeschkin[39] demonstrated involvement of the mitral valve in 86%, aortic valves in 55%, and tricuspid valves in almost 20% of 1024 autopsy specimens from patients with IE. He claimed that mechanical stress was a critical factor in the development of these valvular lesions. Rodbard[40] showed that a Venturi effect was responsible for the observation that the highest yield of bacteria would be found on the low-pressure sink side of a high-pressure jet (left atrial surface of mitral valve in mitral regurgitation, right ventricular side in VSD). The absence of large pressure differences in most cases of large secundum-type atrial septal defects probably explains the rarity of IE in this lesion, as opposed to small VSDs, which have high gradients. Turbulent blood flow damages the endothelium and initiates the formation of platelet and fibrin deposition. This series of events is similar to that seen in the course of primary plug formation with vascular injury.[41] Exposure to cold, high cardiac output states, hormonal manipulations, exposure to high altitudes, and passage of a sterile catheter across a heart valve also have caused initiation of this lesion in animals. Growth of the fibrin and platelet deposition results in the formation of a nonbacterial thrombotic vegetation (NBTV), which is essential in the pathogenesis of endocarditis. Transient bacteremias that occur as a normal part of daily life may cause colonization of the NBTV. As the NBTV grows and adherence of bacteria occurs, an infected vegetation develops. Virulence of different bacteria may directly relate to their ability to adhere to these NBTV. In vitro studies of bacterial colony forming units (CFUs) to determine an "adherence ratio" (cfu bacteria/cfu inoculum) have demonstrated that organisms most likely to cause IE clinically (enterococci, viridans Streptococci, Staph. aureus) adhered to valvular endothelium more readily than organisms rarely responsible for IE.[42] Another factor that may be important in increased virulence is the ability of certain streptococci found in the oral cavity to produce dextran. In fact, more than 50% of the streptococci responsible for IE produce dextran, although the percentage of dextran-producing organisms found in the bloodstream after dental manipulation is far lower.[43] The amount of dextran produced by the bacterial strain also may correlate with virulence.[44] It is unclear how these experimental findings actually relate to disease in humans. Another substance that may be a receptor for certain organisms is fibronectin. This substance is found on the surface of NBTV in polyethylene catheter–induced IE. Organisms such as Staph. aureus, Candida albicans, Strep. sanguis, and Strep. faecalis adhere to fibronectin, while organisms rarely found to cause IE do not.[43]

Once an NBTV is colonized, the size of the vegetation grows by increasing numbers of bacteria as well as by further platelet-fibrin deposition. The colonized NBTV produces a constant bacteremia and reseeding of the circulating organisms onto the already enlarging vegetation. Kissane[45] described three zones in the vegetation: 1) necrotic endocardium; 2) a broad zone of bacteria, pyknotic nuclear debris, and fibrin; and 3) a thin surface coat of fibrin and leukocytes. Proliferation of bacteria in the protected middle zone is relatively unchecked as the normal host defense mechanisms are unable to penetrate into the vegetation and penetration of any circulating antimicrobial agent is diminished.[46] The internal environment of the middle zone of the NBTV is such that

bacterial metabolism is depressed, and thus the action of any antimicrobial that is present is attenuated.

Pathologic changes observed in the heart are secondary to local extension of the infection. Vegetations may be single or multiple and range in size from less than a millimeter to several centimeters. Large lesions may resemble tumors and result in hemodynamically significant stenosis. Certain organisms, including Candida sp., Haemophilus sp., and Staph. aureus, may produce friable lesions that can embolize. Ulceration of tissue, especially heart valves, may result in perforation and produce the onset of sudden congestive heart failure. Other complications include rupture of chordae tendineae, abscesses of the valve ring and fistula formation with the development of pericardial empyema and tamponade, aneurysms of the sinus of Valsalva or ventricle,[47] and myocardial infarction secondary to emboli.[48]

Distant organ involvement secondary to embolic events may occur. One necropsy review of endocarditis in children found the lungs to be the most common site of distant organ involvement.[21] The kidney was the most frequently involved organ on the systemic side of the circulation, with splenic and cerebral infarcts somewhat less common. In other studies, cerebral emboli have been found in 30% of cases of IE in adults and children, with subsequent infarction, abscess, mycotic aneurysm, subarachnoid hemorrhage, and acute hemiplegia of childhood.[49] Microemboli to the cerebral circulation may occur and cause a confused mental state, while strokes are usually secondary to emboli to the middle cerebral artery.[50] Aortic valve infection probably has the highest incidence of embolic complications.[50] The ability to visualize a vegetation by echocardiography, which implies that the vegetation is large, is also probably related to the risk of emboli events.[51,52]

Immunologic mechanisms play an important role in the pathogenesis and sequelae of subacute IE. Cell-mediated and humoral immunity both are active in this disease process. A hypergammaglobulinemic stage usually exists and is due to both polyclonal and antigen-specific B cell activation.[53] Part of the hypergammaglobulinemia is due to circulating rheumatoid factors (RF)[43]; levels of RF may decrease with successful therapy and increase with relapse of disease. Both antibody responses directed at the infecting organism and nonspecific responses have been demonstrated. It is possible that C3b, in conjunction with circulating immune complexes, may bind to the surface of B cells and initiate production of antibodies not primarily directed at the infecting organism. Circulating immune complexes are found with increased frequency in patients with longstanding illness, right-sided disease, hypocomplementemic states, and extravalvular manifestations.[54] Bayer et al.[55] studied 29 patients with culture-proven IE and found that nearly all had levels of circulating immune complexes >12 μg/mL. A mixed-type cryoglobulinemia was noted in 90% of patients with IE.[56] Renal involvement with both focal and diffuse glomerulonephritis has been described and immune complex deposition is found in both conditions.[57–61] In addition, other autoantibodies, including antiendocardial, antisarcolemmal, antimyolemmal, and antinuclear antibodies, are found during the course of IE.[62]

CLINICAL MANIFESTATIONS

The clinical manifestations of IE are highly variable and depend on the underlying pathophysiologic disease processes. The extent of local involvement of the myocardium or valves, embolization from vegetations, and activation of immunologic mechanisms all play essential roles in clinical expression. Patients with acute IE may present in shock and with a clinical picture consistent with overwhelming sepsis. In some cases, confirmation of endocarditis may be found only during autopsy. In the subacute form of the disease, an indolent course may be seen with a diagnosis not established for weeks or months. Since endocarditis frequently occurs in children with underlying heart disease, subtle changes in their physical examination may be missed unless a high degree of suspicion is present on the part of the examiner. Table 90–1 lists the major clinical manifestations of infective endocarditis and their relative frequencies in children.

The most common finding with IE is fever, although it may be absent in up to 10% of cases. It is usually low grade and shows no specific pattern, especially in the subacute form. Other nonspecific complaints including malaise, anorexia, weight loss, fatigue, and sleep disturbances may be present. Involvement of the large joints, with arthralgias or arthritis, occurs in 24% of patients. Nausea, vomiting, and nonspecific abdominal pains are found in 16% of cases. Chest pains, which usually are related to myalgias but are sometimes secondary to pulmonary embolism, especially with tricuspid valve involvement, occur in up to 10% of older children.

The presence of heart murmurs in patients with infective endocarditis has been accepted as a "classic finding." In fact, murmurs usually are present in up to 90% of affected children. However, most of these patients have underlying congenital defects and initially presented with a murmur specific for their lesion. A new or changing murmur occurs in only 25% of children. Frequently, the absence of a changing murmur or the onset of a new murmur in children with pre-existing congenital lesions contributes to the delay in the diagnosis of IE. Congestive heart failure may occur in up to 30% of children and is especially common in those patients who develop a new murmur of valvular insufficiency.

Table 90–1. Symptoms and Physical Findings of Infective Endocarditis*

Symptom/Finding	*Frequency (%)*
Fever	56–100
Anorexia/weight loss	8–83
Malaise	40–79
Arthralgias	16–38
Gastrointestinal distress	9–36
Chest pain	5–20
Heart failure	9–47
Splenomegaly	36–67
Petechiae	10–50
Embolic events	14–50
New/changing murmur	9–44
Clubbing	2–42
Osler's nodes	7–8
Roth spots	0–6
Janeway lesions	0–10
Splinter hemorrhages	0–10

*Based on data from references 22, 39, 78, 94, 163, 171, and 179.

Exacerbation of congestive heart failure in children with rheumatic or congenital lesions who had been previously well controlled on chronic medical therapy should alert the clinician to consider the diagnosis of IE.

Signs and symptoms of neurologic involvement are seen in about 20% of children with IE. The sudden development of a clinical picture consistent with cerebral infarction in a child with an underlying heart defect should suggest the diagnosis. Acute hemiplegia, seizures, ataxia, aphasia, focal neurologic defects, sensory loss, and changing mental status may occur as a presenting feature or even years after the disease process has been treated.[63]

Splenomegaly occurs in about 55% of children with IE. It is usually found in patients with subacute disease and immune system activation. On palpation, the spleen is nontender. Hepatomegaly also is observed in many patients. Infarction of the spleen or abscess formation should be suspected in patients with left upper quadrant pain and tenderness that radiates to the shoulder area. A pleural friction rub or pleural effusion may be observed as well.

Specific skin lesions associated with IE are more common in adults than in children. Petechiae are seen in about a third of cases, especially in patients with a more chronic course. Common sites of involvement are the mucous membranes of the mouth, the conjunctivae, and the skin on the extremities. Petechiae are the most common skin manifestation in IE, occurring in up to 40% of patients; purpura has been reported but is rare.[43,64] Osler's nodes, which also have been described in systemic lupus erythematosus and in extremities distal to the sites of prolonged arterial catheterization, are exquisitely tender lesions. They are most commonly found on the pads of the fingers and toes, the thenar and hypothenar eminences, the sides of the fingers, and the skin on the lower part of the arm.[65] Much controversy still exists over whether Osler's nodes represent an immunologic response to infection manifesting as a vasculitis or whether they are septic emboli. Janeway lesions are differentiated from Osler's nodes in that they are nontender, hemorrhagic plaques that frequently occur on the palms and the soles and represent septic emboli with bacteria, neutrophils, and subsequent necrosis with subcutaneous hemorrhage.[66] Roth spots are small, pale, retinal lesions with areas of hemorrhage usually located near the optic disc. Osler's nodes, Janeway lesions, splinter hemorrhages, and Roth spots occur in only 5 to 7% of children with endocarditis.

Infants and neonates may present with a clinical picture less specific than that seen in older children. The onset is more acute and clinically mimics overwhelming sepsis. The diagnosis rarely is suspected prior to death.[67,68] Early reports concluded that endocarditis occurring in infants was not highly correlated to coexisting congenital heart disease.[69,70] However, more recent studies have concluded the opposite,[67] probably because of the earlier age at palliative or corrective surgery. The presence of indwelling vascular catheters has also increased the incidence of endocarditis in neonates. Persistent bacteremia associated with a deterioration in pulmonary function, coagulopathies, thrombocytopenia, and the appearance of murmurs should arouse suspicion of possible endocarditis in a neonate.

The clinical presentation of infective endocarditis in intravenous drug abusers has several distinctive features. Previous underlying heart disease is found in only one third of patients. The tricuspid valve is the most commonly affected site, and these patients often have pulmonary complications including infarction, abscess formation, and signs and symptoms of pleural effusions. Extracardiac sites of infection also are found in about two thirds of cases.[71] Tricuspid insufficiency with findings of a murmur of tricuspid regurgitation, a pulsatile liver, and gallop rhythm are found in 33% of patients.[72]

COURSE AND PROGNOSIS

The course and prognosis of patients with infective endocarditis is variable and depends on many underlying factors, including the severity of the primary cardiac lesion; the presence of prosthetic material; the infecting organism; the duration of illness prior to diagnosis and initiation of appropriate therapy; and the patient's clinical condition at the time of diagnosis (degree of respiratory, neurologic, and cardiovascular or renal compromise). Infective endocarditis was nearly 100% fatal in the preantibiotic era. At the present time, mortality is between 20 and 30%, due to improved methods of diagnosis and treatment with appropriate antibiotics. Mortality rates are somewhat higher in patients with acute staphylococcal infection, fungal infection, and prosthetic valve endocarditis. Sudden cardiac decompensation owing to congestive heart failure remains the single most important factor affecting mortality. Several studies in adults have directly correlated mortality to uncontrolled congestive heart failure. Mortality may be due to sudden perforation of the aortic valve with severe aortic insufficiency, chordal rupture with resultant mitral regurgitation, or myocardial necrosis with resultant intracardiac shunting through a ventricular or atrial septal defect or through a ventriculoatrial communication. Intramyocardial abscess formation with the development of myocarditis may be an important factor determining ultimate prognosis.[73]

Duration of therapy is dependent on the ability to eradicate the organism from the body. Surgical intervention is sometimes necessary, especially in prosthetic valve endocarditis or abscess formation.

Patients who survive will always be at risk for future development of IE by virtue of their underlying cardiac lesions or from residual damage as a result of their recent infection. Recurrence of disease after an apparently successful course of therapy may occur early (within 3 months of completion of therapy), or late (3 to 6 months after completion of therapy) and should be suspected if fever or other symptoms recur shortly after antibiotics are discontinued. The organism(s) found at relapse may be identical or occasionally different from the organism(s) identified initially.

LABORATORY INVESTIGATION

Table 90–2 summarizes the laboratory findings most commonly seen in children with IE. Blood cultures are the single most im-

Table 90–2. Laboratory Findings*

Finding	*Frequency (%)*
Elevated ESR	71–94
Positive rheumatoid factor	25–55
Anemia	19–79
Positive blood culture	68–98
Hematuria	28–47

*Based on data from references 22, 39, 78, 94, 163, 171, and 179.

portant diagnostic technique in establishing the diagnosis of IE. The wide spectrum of organisms that may be responsible for the infection dictates that scrupulous aseptic technique be utilized to assure that skin contaminants are not introduced into the blood sample. Bacteremia usually is continuous and low grade so that the timing and site of collection does not increase the yield.[74] In approximately 66% of all cases of IE, all blood cultures will grow the infecting organism[75]; in 90% of cases the first two blood cultures will be "positive." If a patient has received antibiotics prior to blood testing, the chance of obtaining a positive culture may be reduced from 95 to 100% to 64%.[22] When pretreatment has occurred, placing the blood sample into hypertonic media may enhance the chance of isolating the organism. Patients with fungal endocarditis may have only intermittently positive blood cultures. The organism may take one week or longer to grow in culture.[76]

Ideally, three to five sets of blood cultures should be obtained within the first 24 hours. These specimens should be obtained from different sites and contain from 3 to 5 mL of blood each. Thioglycollate broth should be used and the bottles kept for 3 weeks in order to detect slow-growing organisms. Nutritionally variant streptococci should be suspected if a Gram positive coccus is isolated in broth but fails to grow in subculture. The organism should then be subcultured onto media enriched with pyridoxal phosphate or L-cysteine.[77]

Blood cultures may be negative in 10 to 15% of cases of suspected endocarditis. Negative cultures may occur due to 1) prior administration of antibiotics; 2) endocarditis due to rickettsiae, chlamydiae, or viruses; 3) slow-growing (Candida sp., Haemophilus sp., Brucella sp.) organisms or nutritionally variant streptococci; 4) infections due to anaerobic organisms; 5) nonbacterial thrombotic vegetation endocarditis; 6) mural endocarditis; 7) right-sided endocarditis; 8) fungal endocarditis (esp. Aspergillus sp.); and 9) incorrect diagnosis.[78–80] Examination of the buffy-coat layer of peripheral blood may demonstrate the presence of bacteria within leukocytes. Additional sites including urine, sputum, cerebrospinal fluid, synovial fluid, bone marrow, and lymph nodes may be infected concomitantly. Thus, cultures of these additional sites may be included if blood cultures fail to demonstrate an infecting agent. Histologic examination of a surgical specimen, with proper staining techniques for bacteria and fungi, may also aid in diagnosis.

Adjunctive laboratory tests include the erythrocyte sedimentation rate (ESR), which is elevated in up to 90% of patients and correlates with the hypergammaglobulinemia found in this disease. An artifactually low ESR may be found with renal disease, severe congestive heart failure, or polycythemia. The ESR should decrease toward normal if therapy has been successful, and serial measurements may be helpful in monitoring therapy. A positive rheumatoid factor (RF) has been found in one fourth to one half of pediatric patients with IE and may be supportive evidence for the diagnosis when cultures are negative. Serial measurement of RF can be also used to monitor the adequacy of therapy in these patients.[81] Immune complex–mediated glomerulonephritis may result in hypocomplementemia. Anemia, usually due to a chronic disease state, is found in 40% of patients. Since children with cyanotic congenital heart disease frequently develop IE, the finding of a normal or slightly high hemoglobin level should raise the suspicion of anemia. Although leukocytosis is not uncommon, leukopenia may occur in acute cases with overwhelming sepsis. Microemboli and consequent microinfarcts in the kidney produce hematuria, with or without proteinuria, casts, and bacteremia, in 25 to 50% of cases.

Circulating immune complexes, as measured by either the Raji-cell radioimmunoassay[82] or ^{125}I-Clq binding assay,[83] are present in the majority of adults with IE, although they may be conspicuously absent in acute disease.[84] Immune complexes also may be found in septicemia and in up to 10% of normal adult controls. Several authors[55,85,86] have used the level of circulating immune complexes to differentiate endocarditis from septicemia and have used serial measurements to monitor therapeutic success. Levels of immune complexes >12 μg/mL occurred in 28 of 29 patients with culture-proven endocarditis.[55] However, one study of staphylococcal disease was unable to differentiate patients with endocarditis from bacteremic patients based on levels of immune complexes.[87] Though there have been few studies of circulating immune complex levels in children with IE, elevated levels have been found in some patients.[4,88]

Serologic testing for specific organisms may be helpful in culture-negative endocarditis. Antibodies against teichoic acids, which are major components of the cell wall in Staphylococcus aureus, may be present in 85% of adults with IE although the false-positive rate may be as high as 10%.[89–91] A teichoic acid antibody titer of $>1:1$ in a bacteremic adult patient correlates with deep-seeded infections including but not restricted to endocarditis. However, teichoic acid antibody levels do not differentiate the type of deep-seeded infection. As with circulating immune complexes, serial measurements of teichoic acid antibody levels may correlate with successful therapy. Unfortunately, no data exist concerning teichoic acid antibody levels in children with IE.

ECHOCARDIOGRAPHY

The role of echocardiography in helping to establish the diagnosis of IE has grown considerably because the technology has improved vastly since single crystal M-mode techniques were first introduced. Generally, the two-dimensional (2-D) technique is superior to the M-mode technique in the investigation for vegetative lesions. Some areas of the heart, such as the pulmonary valve, are better visualized using 2-D imaging, and the increased sensitivity of this technique with pulmonary valve endocarditis has been well documented.[92,93] The value of 2-D echocardiography in prosthetic valve endocarditis also is superior to that of M-mode. An echo-free space found in more than one tomographic plane has aided the diagnosis of perivalvular abscess[94] (which may complicate native valve endocarditis in up to 30% of cases, and more frequently in prosthetic valve endocarditis), and adjunctive use of Doppler technique to diagnose prosthetic valve regurgitation before it becomes clinically apparent may aid in earlier diagnosis. The sensitivity of echocardiography in detecting vegetative lesions in suspected endocarditis in adults ranges from 13 to 83%,[95,96] with the more recently published series utilizing 2-D technique exhibiting a greater sensitivity.

How the detection of echocardiographically proven vegetations correlates with morbidity and/or mortality is somewhat controversial. Some authors[97,98] have concluded that the detection of vegetations, especially if left-sided, may help to establish a subgroup of patients who would benefit by early surgical intervention.

Buda et al.[98] found vegetations on 21 of 50 (42%) adults with IE. Of interest is that most of the IV drug abusers with IE did not have detectable vegetations. They concluded that patients with a "positive echo" were twice as likely to develop serious complications, usually emboli, more commonly cerebral than peripheral, and that if the vegetation was >1 cm^2, patients were at higher risk for death or severe CHF, and more frequently required surgical intervention. However, the risk of embolization was not correlated with vegetation size. These findings are in accord with several other studies.[51,99–101]

In a study of 15 children with IE using both M-mode and 2-D technique, vegetations were detected in 10 of 15 (66%) of patients.[97] Of those 10 patients, three had systemic emboli and two died, while none of the patients without an echo-proven vegetation had an embolic complication. The authors suggested that echocardiography may help to identify a high-risk population that would benefit from surgical intervention. Some authors[102] have suggested that the size and mobility of a vegetation may be useful in differentiating bacterial from fungal endocarditis. However, in our experience, this claim is probably not valid inasmuch as large vegetations may frequently be seen in bacterial or fungal endocarditis.

On the other hand, a negative echocardiographic study does not rule out the presence of vegetations.[103] The resolution on most equipment limits the detection of vegetations to those greater than 2 to 3 mm in size. Poor technique also may hinder evaluation. Rheumatic heart disease with pre-existing valve disease, mitral valve prolapse with thickened leaflets, marantic vegetations, Loeffler's endocarditis, and Chiari networks in the right atrium and valve ring abscesses all pose interpretive problems to the echocardiographer.[104]

Once a vegetation is detected, it may show no significant change during therapy. Therefore, a recurrence of disease cannot be diagnosed unless a noticeable increase in size has occurred or a new vegetation appears.[104] Attempts to estimate serially the size of a vegetation are fraught with technical and interpretive error and probably of little value. However, continued growth of a vegetation coexistent with persistent bacteremia or evidence of further endocardial infiltration may indicate a treatment failure and/or the need for surgical intervention.[104–106] Examination of an echocardiogram at the time of hospital discharge of a patient after an apparently successful course of antibiotic therapy would be used as a baseline for that patient in further evaluation.

ELECTROCARDIOGRAPHY

Numerous electrocardiographic abnormalities may be found throughout the course of IE. Ventricular ectopy[107] in patients with hemodynamic compromise may be life-threatening. Atrial fibrillation has been reported[107,108] in both adults and children and may be secondary to atrioventricular valve regurgitation. Extension of abscess formation or the inflammatory response may cause direct injury to the conduction system. Complete right bundle branch block, left anterior or posterior fascicular block, and complete atrioventricular block have all been reported.[109] Abscess formation in the perivalvular aortic region may directly injure the atrioventricular node because of its close anatomic location to that structure. This may result in sudden death unless temporary and eventually permanent pacing is instituted.[110] One autopsy study of 125 patients with IE and cardiac abscess formation demonstrated conduction defects in 14 of 25 patients with nine deaths despite attempts at temporary pacing.[110]

PROPHYLAXIS

The use of antibiotics prior to and during any procedure that induces a transient bacteremia has become standard medical practice for the prevention of IE. However, the literature contains numerous reports of failures with subsequent development of endocarditis.[111] Although many times failure is related to inappropriate drug regimens, occasionally infection develops despite adherence to published guidelines. In an an attempt to consolidate current opinion on appropriate antibiotic regimens for endocarditis prophylaxis, the American Heart Association's Council on Cardiovascular Diseases in the Young Committee on Rheumatic Fever and Bacterial Endocarditis published recommendations in 1985 (Table 90–3).[112]

Numerous theories have been proposed to explain how antibiotics given prophylactically prevent endocarditis. Two possibilities are 1) that the antibiotic reduces the magnitude of a bacteremia associated with a procedure, and 2) that bacterial adherence mechanisms are altered such that a nidus of infection would be unlikely to develop. Hess et al.[113] examined the incidence of bacteremia after dental extraction in 82 children with cardiac disease who received penicillin prophylaxis. They found an incidence of 21%, half of which were streptococcal species. This compares with previous reports that noted a 0 to 53% incidence.[112] Interestingly, 6% of the isolated organisms were anaerobic. In addition, a number of penicillin-resistant organisms were found, although no child developed endocarditis. The authors hypothesized that although bacteremias still occurred, the microbial adherence was adversely affected by the antibiotics. This is supported by a recent rat model study that studied the effects of single-dose amoxicillin and erythromycin after the development of sterile aortic vegetations.[114] In this model, periodontally diseased teeth were extracted to produce a bacteremia similar to the conditions that might occur in human beings during dental manipulation. Endocarditis developed in 89% of the control group (vegetations but no prophylaxis). The organisms cultivated from the rat's dental plaque were identical to those found in blood culture, confirming the relationship between extraction and seeding of the vegetation. The incidence of bacteremia was nearly the same in the control group as in the treated group; however, essentially none of the treated group developed endocarditis. Another experiment, using rats with catheter-induced aortic vegetations, demonstrated a higher incidence of postextraction endocarditis in animals with periodontal disease as compared to those with healthy dentition. In this study, there was no correlation between the incidence of IE and the degree of bacteremia, suggesting that the rats with periodontal disease were at higher risk for other reasons not elucidated.[115]

Special circumstances arise concerning the use of antibiotic prophylaxis. Tables 90–4 and 90–5 list various conditions and procedures and the infecting organisms responsible for the development of IE in both children and adults. In patients requiring multiple dental procedures who have recently received antibiotic prophylaxis, oral streptococci with reduced susceptibility may flourish and possibly result in ineffective prophylaxis. Whereas giving 3 g of amoxicillin once per week does not result in a high

Table 90–3. Recommended Antibiotic Regimens for Endocarditis Prophylaxis in Children*

Regimen	*Condition*	*Dosage*
Dental/Respiratory Tract Procedures		
Standard	Dental procedures that cause gingival bleeding; oral or respiratory tract surgery	Penicillin V (1.0–2.0 g orally 1 hr before the procedure, then 0.5–1.0 g 6 hr later); for patients unable to take oral medications, 1–2 million units of aqueous penicillin G IV or IM 30–60 min before the procedure and 0.5–1.0 million units 6 hr later
Special	Parenteral regimen for use when maximal protection desired, i.e.: for patients with prosthetic valves	Ampicillin (50 mg/kg IM or IV) plus gentamicin (2.0 mg/kg IM or IV) one-half hour before the procedure, followed by 0.5–1.0 g oral penicillin V 6 hr later; alternatively, parenteral regimen may be repeated once 8 hr later
	Oral regimen for penicillin-allergic patients and those on rheumatic fever prophylaxis	Erythromycin (20 mg/kg orally 1 hr before the procedure, then 10 mg/kg 6 hr later)
	Parenteral regimen for penicillin-allergic patients and those on rheumatic fever prophylaxis	Vancomycin (15–20 mg/kg IV) 1 hr before the procedure; no followup dose is necessary
Gastrointestinal/Genitourinary Procedures		
Standard	Genitourinary/gastrointestinal tract procedures	Ampicillin (50 mg/kg IM or IV) plus gentamicin (2.0 mg/kg IM or IV) given 30 min to 1 hr before procedure; 1 follow-up dose may be given 8 hr later
Special	Oral regimen for minor or repetitive procedures in low-risk patients	Amoxicillin (50 mg/kg orally 1 hr before the procedure and 50 mg/kg 6 hr later)
	Penicillin-allergic patients	Vancomycin (15–20 mg/kg IV) plus gentamicin (2 mg/kg IM or IV) 1 hr before the procedure; may be repeated once 8 hr later

*From Shulman, S.T., et al.: Prevention of bacterial endocarditis: A statement for health professionals by the Committee on Rheumatic Fever and Bacterial Endocarditis of the Council on Cardiovascular Diseases in the Young of the American Heart Association. Am. J. Dis. Child., *139*:232, 1985.

incidence of resistant streptococci, erythromycin given at the same dosage may result in a significant number of resistant organisms.[116] Therefore, if prophylaxis is required twice in a month, amoxicillin can be given as recommended. In penicillin-allergic patients who require erythromycin, the interval between dental procedures should be increased if possible. If a dental abscess is found in a patient presently undergoing treatment for IE, it should be surgically drained.

Patients who develop a condition that must be surgically treated while being treated for IE should receive additional prophylaxis specific for the area of surgical interest and in accord with the published recommendations. It is also important to remember that patients receiving penicillin for rheumatic fever prophylaxis should receive additional prophylaxis as noted above.

Elective surgery, for whatever reason, should be postponed until treatment of active IE is completed. Other special circumstances that require prophylaxis include the presence of permanent transvenous pacing leads, cerebral ventriculoatrial shunts, and arteriovenous shunts.[112]

The use of antibiotic prophylaxis in patients with mitral valve prolapse (MVP) is controversial. This condition exists in approximately 5% of the U.S. population.[117,118] A case–control study comparing persons with MVP to normal controls found that the odds ratio for the association of IE with MVP was 8.2, and that it increased to 15.2 when a mitral regurgitation murmur was present.[119] Other studies have found similar risks.[120] A recent study attempted to define the absolute risk—the chance of developing IE over a time period—rather than the relative risk.[118] The group with MVP and no mitral regurgitation had an absolute risk for the development of IE of 0.0046% (one person in 21,950 persons per year) as compared to 0.520% (one person in 1920 per year) in the group with MVP and mitral regurgitation. Therefore, over a 50-year period, 26 of 1000 patients with MVP and mitral regurgitation would develop IE. However, only two of 1000 patients with MVP without mitral regurgitation would develop IE, which is not significantly greater than the risk to the general population. The authors of this study suggest that routine prophylaxis should be used only in patients with MVP and mitral regurgitation. This study also showed that male gender and age greater than 45 years were independent risk factors for the development of IE in patients with MVP, suggesting that they would receive added benefit from routine antibiotic prophylaxis.

Unfortunately, not many reports on the natural history of MVP in children address the risk of developing IE. None of the 30 children with MVP followed by Frand[121] for an average of 4 to 5 years developed IE, indicating no additional risk for this lesion. However, the relatively short duration of followup should preclude such a firm conclusion. Duren et al.[122] prospectively followed 300 patients with MVP with a mean followup of 6.1 years. They found a 6% incidence of IE, which accounted for 15% of all serious complications in these patients. Though the study design has been criticized,[123] including the lack of a control group, the mortality and morbidity that occurred in Duren et al.'s patients deserves

Table 90–4. Conditions and Procedures Related to Endocarditis Prophylaxis*

Cardiac Conditions for Which Endocarditis Prophylaxis Is Recommended
Prosthetic cardiac valves (mechanical and biosynthetic)
Most congenital cardiac malformations
Surgically constructed systemic–pulmonary shunts
Rheumatic and other acquired valvular disease
Idiopathic hypertrophic subaortic stenosis
History of bacterial endocarditis
Mitral valve prolapse with insufficiency
Foreign material in the heart
Cardiac Conditions for Which Endocarditis Prophylaxis Is Not Recommended
Isolated secundum atrial septal defect
Secundum atrial septal defect repaired without a patch 6 or more months earlier
Patent ductus arteriosus ligated and divided 6 or more months earlier
Procedures for Which Endocarditis Prophylaxis Is Recommended
All dental procedures likely to induce gingival bleeding
Tonsillectomy and/or adenoidectomy
Surgical procedures or biopsy involving respiratory mucosa
Bronchoscopy, especially with a rigid scope
Incision and drainage of infected tissue
Selected genitourinary and gastrointestinal procedures (cystoscopy, urethral catheterization, urinary tract surgery, gallbladder or colonic surgery, esophageal or anal dilatation, colonoscopy, upper GI tract endoscopy with biopsy, proctosigmoidoscopic biopsy)
Cardiac surgery
Procedures for Which Endocarditis Prophylaxis Is Not Routinely Recommended
Orotracheal intubation
Cardiac catheterization
Cesarean section
Therapeutic abortion
Intrauterine device insertion or removal

*From Shulman, S.T., et al.: Prevention of bacterial endocarditis: A statement for health professionals by the Committee on Rheumatic Fever and Bacterial Endocarditis of the Council on Cardiovascular Diseases in the Young of the American Heart Association. Am. J. Dis. Child., *139*:232, 1985.

serious consideration. Seven of the 18 patients in that study developed their infection after a dental procedure without prophylaxis.

The intermittent nature of the auscultatory click associated with some cases of MVP implies that the regurgitation associated with this lesion may be intermittent as well. Until further data concerning the exact incidence of mitral regurgitation associated with MVP in children is available, we believe that the safest course is to prescribe routine SBE prophylaxis for all children who have documented MVP.

MICROBIOLOGY

Many different organisms have been associated with IE in human beings. Table 90–6 lists the most common causative agents responsible for the development of IE. Gram-positive cocci are the causative agents in 90% of cases in which an organism is isolated. Streptococci, especially of the viridans group, remain the bacteria isolated most frequently. However, due to the increasing role of surgery and prosthetic material in the correction and palliation of congenital heart disease, the percentage of cases caused by staphylococci, Gram-negative bacilli, and fungi has increased.[3,68,124] Identification of the causative agent is the single most important procedure to confirm the diagnosis, direct therapy, and predict outcome and possible complications.

Streptococci

Streptococci are a heterogeneous group of organisms. There are different systems of classification that depend on several features, including patterns of hemolysis observed in blood agar plates, biochemical reactions, growth characteristics, antigenic reaction, and serologic relatedness. The least discriminating system uses the type of hemolysis produced by a strain of streptococcus when grown on a blood agar plate: beta hemolysis is a clear zone surrounding each colony caused by complete blood cell lysis; gamma hemolysis designates no detectable hemolysis; and alpha hemolysis is an inner layer of unhemolyzed cells and an outer layer of hemolyzed cells that produce a greenish discoloration in the medium. The term "viridans" streptococci refers to the majority of strains that are alpha hemolytic, although other strains such as the pneumococcus also may be alpha hemolytic. The group viridans streptococci is made up of many different species with varied biochemical properties and biologic behaviors. For instance, the viridans streptococcus, Strep. milleri, is especially virulent and causes a high incidence of suppurative intracardiac and extracardiac complications in patients with endocarditis.[125,126] When a viridans streptococcus is isolated from a patient with endocarditis, it may be valuable for the laboratory to perform species determination. The most common viridans streptococci isolated from adults with infective endocarditis are Strep. sanguis, Strep. bovis, Strep. mutans, and Strep. mitior.[127]

The Lancefield typing system[128] was devised to differentiate beta hemolytic streptococci into serogroups by means of antigenic differences in cell wall carbohydrates. Certain alpha and gamma hemolytic strains also contain group-specific antigen, such as enterococci that contain Group D cell wall carbohydrates. Therefore, viridans streptococci may be Lancefield typeable or nontypeable.

The viridans streptococci are the most common causative agents in childhood IE, accounting for about 40% of cases. These organisms are part of the indigenous flora of the mouth and gastrointestinal tract. Any procedure, such as dental surgery or extraction, that disrupts the mucosal integrity in these areas predisposes the patient to bacteremia with viridans streptococci. These organisms commonly cause endocarditis in patients with underlying heart disease, but are less common as causes of postoperative infection. Although viridans streptococci usually are associated with a more indolent, subacute clinical presentation, they can cause acute, rapidly progressive disease.[129] Most strains of viridans streptococci are exquisitely susceptible to penicillin, although prior antibiotic administration may promote infection with resistant strains. Recurrences and treatment failures are rare, but may occur.[130]

Nutritionally variant viridans streptococci are being recognized increasingly as the causative agent of IE in children.[10,131,132] The organism will grow in broth, but will not grow in subculture unless L-cysteine or pyridoxine is added to the media. These organisms must be looked for in every case of "culture-negative" endocarditis.

The enterococcus is an unusual strain of streptococci because

Table 90–5. Procedures Associated with Bacteremia in Children and Adults*

Procedure	*Associated Organism*	*Positive Blood Cultures (%)*
Dental extraction	Streptococcus, Diphtheroids	30–65
Chewing gum, candy	Streptococcus, Staph. epidermidis	0–51
Brushing teeth	Streptococcus	0–26
Tonsillectomy	Streptococcus, Haemophilus, Diphtheroids	28–38
Bronchoscopy (rigid scope)	Streptococcus, Staph. epidermidis	15
Bronchoscopy (flexible scope)		0
Nasotracheal intubation/suctioning	Streptococcus, aerobic Gram-negative rods	16
Orotracheal intubation		0
Sigmoidoscopy/colonoscopy	Enterococcus, aerobic Gram-negative rods	0–9.5
Upper GI endoscopy	Streptococcus, Neisseria, Staph. epidermidis, Diphtheroids, other	8–12
Percutaneous liver biopsy	Pneumococcus, aerobic Gram-negative rods, Staph. aureus, other	3–14
Urethral catheterization	Not stated	8
Manipulation of Staph. aureus suppurative foci		54

*From Everett, E.D., and Hirschmann, J.U.: Transient bacteremia and endocarditis prophylaxis: A review. Medicine, *56*:61, 1977.

it is much less susceptible to penicillin; successful treatment requires use of an additional antibiotic, usually gentamicin in children. Enterococcal endocarditis is less common in children than adults, accounting for only 4% of pediatric cases.[133] This strain inhabits the gastrointestinal and genitourinary tracts and may enter the bloodstream after instrumentation to these areas. While 40% of adult patients with enterococcal endocarditis have no underlying heart disease,[72] affected children rarely have previously normal hearts. Endocarditis should be considered in all infants and children with unexplained enterococcal bacteremia.

The pneumococcus is an alpha hemolytic streptococcus, but the clinical presentation of pneumococcal endocarditis is usually different from endocarditis carried by viridans streptococci. In the preantibiotic era, the pneumococcus accounted for 10 to 15% of cases of endocarditis, but now causes less than 2%.[134] Pneumococcal endocarditis may have a predilection for the mitral valve.[135] Approximately one half of cases of pneumococcal endocarditis occur in persons without underlying heart disease.[136] The clinical course usually is acute and fulminant, with valvular dysfunction and cardiac decompensation occurring frequently. Early surgical intervention usually is required, since the mortality rate with medical management alone is 75%.[134]

Endocarditis caused by β-hemolytic streptococci also was more common in the preantibiotic era than today. The majority of cases are due to Lancefield groups B and G strains,[137,138] whereas group C and A strains rarely cause endocarditis.[139,140] Group B streptococcal endocarditis may lead to large, bulky vegetations and arterial thrombi, which may be easily detected by echocardiography.[141] Noncardiac underlying conditions may include diabetes mellitus, pregnancy, intravenous drug abuse, genitourinary disease, and alcoholism. Mortality may approach 50%.

Table 90–6. Causative Agents in Pediatric Infective Endocarditis*

Organism	*Frequency (%)*
Streptococci	
Viridans	17–72
Enterococci	0–12
Pneumococci	0–21
β-hemolytic	0–8
Staphylococci	
Staph. aureus	5–40
Staph. epidermidis	0–15
Gram-negative aerobic bacilli	0–15
Fungi	0–12
Miscellaneous	0–10
Culture negative	2–32

*Based on data from references 22, 28, 39, 76–78, 94, 114, 163, 171, 179, and 195.

Staphylococci

Staphylococci are responsible for 20 to 30% of cases of IE in children, and the incidence is rising. The majority are due to coagulase-positive Staph. aureus, but coagulase-negative staphylococci are causing an increased number of post–cardiac surgery infections. Staph. aureus may attack previously normal heart valves as well as normal cardiac structures. It is the most likely cause of acute endocarditis in a previously normal child. The course is often fulminant, with frequent suppurative complications both in the heart (myocardial abscess, pericarditis, valve ring abscess) and in other organs.[142] Staph. aureus causes more than 50% of cases of endocarditis in intravenous drug abusers,[124] but the disease in this group of patients tends to be less severe than endocarditis due to other bacterial organisms.[143] The origin of the infecting strain is thought to be the addict's own nose or skin, not the injection paraphernalia.[144] Endocarditis associated with indwelling vascular catheters or prosthetic heart valves frequently is caused by Staph. aureus bacteremia, even if a peripheral focus of infection is present.[145] Treatment of Staph. aureus endocarditis has been complicated by the recent emergence of methicillin-

resistant strains, which may require synergistic antibiotic combinations, such as vancomycin and rifampin, for cure.[146]

The incidence of endocarditis caused by coagulase-negative staphylococci, usually Staph. epidermidis, also is rising rapidly. These organisms rarely cause infective endocarditis in persons without underlying heart disease, but are common causative agents of endocarditis following cardiac surgery.[147,148] Coagulase-negative staphylococci are the major responsible agents in prosthetic valve endocarditis, causing 25 to 67% of early cases and 25 to 33% of late cases.[31,149,150] These organisms can be locally invasive. The mortality rate of Staph. epidermidis prosthetic valve endocarditis with no valve replacement may approach 75% in adults.

Gram-Negative Organisms

Gram-negative bacteria are responsible for 4 to 5% of pediatric cases of endocarditis. However, the percentage of children with Gram-negative bacteremia who develop endocarditis is low. Burn patients, immunosuppressed hosts, recipients of prosthetic heart valves, and narcotic addicts are at increased risk for Gram-negative enteric bacteremia.[151,152] Many species of Gram-negative enteric organisms have caused infective endocarditis in children, but no clear pattern has emerged since data are limited to case reports and general medicine reviews. Morbidity and mortality are high, with frequent development of large vegetations, embolic complications, and cardiac decompensation. Endocarditis should be suspected in any patient with Gram-negative infection when bacteremia persists despite appropriate antibiotic therapy, especially if an unexplained heart murmur and anemia develop. However, in the early postoperative period after cardiac surgery, sustained Gram-negative bacteremia commonly is secondary to other foci of infection (i.e., urinary tract) and does not imply the presence of endocarditis.[153]

Pseudomonas sp. endocarditis is especially difficult to treat, with a high mortality rate.[154] Most patients with this type of endocarditis abuse intravenous drugs.[155] Major embolic complications and congestive heart failure are common.

Other Gram-negative organisms associated with infective endocarditis are the so-called HACEK Coccobacilli: Haemophilus sp., Actinobacillus sp., Cardiobacterium sp., Eikenella sp., and Kingella sp. This group caused 57% of cases of Gram-negative endocarditis seen at the Mayo Clinic from 1958 to 1979.[156] Endocarditis due to Haemophilus influenzae has been reported in several children,[157,158] but infections due to H. aphrophilus and H. parainfluenzae are more common.[159–162] A similar organism, *Streptobacillus moniliformis,* also has been linked to endocarditis.[163] Infective endocarditis in children due to other organisms of the HACEK group is extremely rare.[164,165] The infection usually occurs in the setting of pre-existing valvular disease and runs a subacute course. Embolic phenomena and central nervous system complications are common.[160] All HACEK organisms are fastidious, and may require 2 to 3 weeks for primary isolation, needing subculture onto chocolate agar in 5 to 10% CO_2 for optimal growth. These organisms should be considered in all presentations of "culture-negative" endocarditis.

In the preantibiotic era, Neisseria gonorrhoeae was responsible for 10% of cases of infective endocarditis. However, less than 40 cases have been reported since 1942.[166] The onset usually is acute. It tends to attack previously normal valves, valve replacement is frequently necessary. Nonpathogenic Neisseria sp. are isolated more frequently in endocarditis than gonococci, but these organisms usually attack abnormal or prosthetic valves.[167–169]

Gram-Positive Bacilli

Corynebacterium sp. are unusual causative agents of infective endocarditis, but may occur on either normal or abnormal heart valves.[170] Both toxigenic and nontoxigenic strains of C. diphtheriae can cause endocarditis in children.[171–173] Listeria monocytogenes endocarditis is rare in children and has a high mortality. However, unlike other forms of listeriosis, it is not seen frequently in immunocompromised hosts,[1] and has not been associated with listeriosis in neonates. Fewer than 30 cases of Lactobacillus sp. endocarditis have been described.[174] This infection usually follows dental manipulation in a person with underlying heart disease. Embolic phenomena are common, but treatment usually is successful if appropriate antibiotics are used.

Fungi

The most common predisposing conditions for fungal endocarditis in children are cardiovascular surgery, prolonged antibiotic usage, and the presence of an indwelling intravenous catheter. Most infections are caused by Candida albicans, but other species including, C. tropicalis, C. stellatoides, C. krusei, C. parapsilosis, and C. quilliermondi, have been implicated.[175] Endocarditis caused by intravenous drug abuse is more frequently caused by species other than C. albicans.[176] The clinical course usually is subacute. Embolic phenomena are extremely common and may be the first clinical indication of infection.[177] Large, friable vegetations occur frequently.[178] Ocular and cutaneous manifestations may aid in the diagnosis.[30] The prognosis of Candida sp. endocarditis is poor, related to the propensity for septic emboli to major organs, the tendency for invasion into the myocardium, and the poor penetration of antifungal agents into the vegetations. Diagnosis may be delayed by the tendency for negative or only intermittently positive blood cultures. Successful therapy usually requires surgical intervention.

Aspergillus sp. are the second most frequent cause of fungal endocarditis in children.[179,103] Most patients have had underlying heart disease and recent cardiac surgery, although normal valves can be affected.[180] The most frequent manifestations are fever and emboli, especially to the central nervous system.[181] Only four cases in children have been diagnosed antemortem, three by culture of peripheral emboli. Blood cultures usually are negative. Surgical removal of all infected material is recommended, although only one child has been treated successfully.

Other fungi that rarely cause infective endocarditis include Histoplasma capsulatum, Coccidioides immitis, Cryptococcus neoformans, Torlopsis glabrata, Hormodendrum sp., Mucor sp., Paecilomyces sp., Phialophora sp., and Chrysosporium sp.[182]

Other Organisms

Anaerobic bacilli cause 1% of cases of IE in adults.[183] However, reports of anaerobic endocarditis in children are exceedingly rare.[184]

Infective endocarditis caused by Coxiella burnetti (Q fever) has been documented in over 100 cases, including several children.[185] Clinical manifestations, including anemia, hepatosplenomegaly, fever and intracardiac vegetations, are similar in children and adults. Diagnosis is confirmed by serologic and immunohistologic

investigation. Although Q fever has been documented in the United States,[186] it is much more common in England, Australia, and France.

TREATMENT

Several general principles provide the basis of treatment of IE. The preferable route of antibiotic administration is intravenous. Oral antibiotics may be poorly or erratically absorbed, especially in infants, and often result in treatment failure. A course of at least 4 and up to 6 weeks or longer is required to sterilize vegetations and prevent relapse. Bacteriostatic agents are contraindicated and may lead to failure or relapse if used. Synergism between certain agents may produce a rapid bactericidal effect and allow smaller doses of each drug to be administered, thereby reducing possible toxic side effects. However, certain drug combinations, such as penicillin and chloramphenicol, may be antagonistic.

After initiation of therapy, daily blood cultures should be obtained. Although negative blood cultures do not necessarily correlate with a therapeutic success, continued positive blood cultures usually indicate the need to investigate the serum concentration of the drug in the patient, to add another agent, or to change therapy. If the patient has not responded clinically to initial antibiotic therapy within several days, additional blood cultures should be obtained. In addition, attention to the patient's clinical course is essential. Patients usually begin to improve within a few days of initiating appropriate therapy, although persistent fever may occasionally occur in patients with an eventual good outcome. Electrocardiographic monitoring should be performed in the early stages of therapy to assess the presence of arrhythmias or the development of conduction disturbances that may require immediate attention. If second-degree atrioventricular block develops during an episode of endocarditis, temporary transvenous pacing should be considered. Pacing should always be instituted for third-degree atrioventricular block. Physical examination to assess development of regurgitant murmurs or embolic events is also mandatory.

Current recommendations for optimal therapy in pediatric patients with IE are based largely on studies from adult patients. These regimens usually are more successful and less toxic in children than in adults (Table 90–7).

The timing of therapy generally depends on the patient's clinical condition. In a case of suspected IE in a seriously ill child, empiric therapy should begin immediately after obtaining the appropriate blood cultures. In patients in whom Staph. aureus infection is probable (acute presentation, IV drug abusers) a penicillinase-resistant penicillin should be added to the usual regimen of penicillin G and an aminoglycoside. The latter two agents would be employed in a patient with a subacute presentation and would be appropriate for viridans streptococci, enterococci, and most Gram-negative organisms. Patients who have recently undergone cardiac surgery should receive vancomycin in addition to an aminoglycoside because of the high incidence of hospital-acquired Staph. epidermidis, which may be resistant to methicillin or nafcillin. Once the blood cultures have been examined for sensitivity to various antibiotic agents, therapy may be appropriately tailored for the patient.

Several tests are available to determine how sensitive an organism is to treatment with antimicrobials. The minimal inhibitory concentration (MIC) is defined as the lowest concentration of the agent that prevents visible growth, usually in broth, after incubation for 18 to 24 hours. The minimal bactericidal concentration (MBC) is defined as the lowest concentration of the agent that results in either sterilization or a decline of bacterial count of 99.9 percent. Monitoring the inhibitory and bactericidal activity of the patient's serum is controversial. The Schlicter test is an in vitro determination of the maximal serum inhibitory and serum bactericidal levels specific for an infecting organism.[187] However, standardization of this test among different laboratories is poor, creating problems with interpretation.[188] Studies in rabbits with experimentally induced endocarditis show that bactericidal titers of 1:8 or greater usually correlate with therapeutic success.[189] However, in human beings with IE, no similar correlation was seen at titers of 1:8.[190] Although no formal recommendation exists, prospective studies[187] suggest that therapy should be tailored to achieve peak titers of 1:64 or greater and through titers equal to or greater than 1:32. The Kirby-Bauer disc sensitivity test is neither reliable nor quantitative and should not be used to guide therapy. Most viridans streptococci, Strep. pyogenes, Strep. pneumoniae, and nonenterococcal group D streptococci have an MIC for penicillin of less than 0.2 μg/mL in broth. Resistance, as defined by organisms with a MIC ≥0.2 μg/mL, occurs in about 15 to 20% of viridans streptococci. Tolerance occurs when growth of the organism is inhibited (a MIC to penicillin of less than 0.1 μg/mL) and the MBC is greater than eight times the MIC. Treatment failure may result when penicillin is used as the sole agent and organisms become tolerant to therapy.[191] Streptomycin and gentamicin each act synergistically with penicillin or vancomycin in vitro[61] and have been shown to be effective in eradicating vegetations in rabbits with experimentally induced endocarditis.[192]

In adults with IE caused by penicillin-sensitive viridans streptococci, an unacceptable relapse rate is obtained when penicillin is used alone for 2 weeks. However, when intramuscular procaine penicillin and streptomycin are given together for 2 weeks, 99% of patients are cured, a rate identical to a 4-week course of penicillin agents alone[193] or penicillin for 4 weeks with streptomycin administered concomitantly during the first 2 weeks.[194,195] The most cost effective and preferred therapy for uncomplicated penicillin-sensitive streptococcal endocarditis in young adults is the 2-week penicillin–streptomycin regimen.[72] Patients in renal failure or at risk for streptomycin-induced ototoxicity should receive 4 weeks of penicillin. In adults with a complicated course, prosthetic valve endocarditis, infections due to relatively penicillin-resistant organisms, or with symptoms for more than 3 months,[196] penicillin with the addition of streptomycin during the first 2 weeks is recommended. Gentamicin is preferred in pediatric patients because of its lower ototoxicity as compared with streptomycin. We reemphasize, however, that none of these regimens has been evaluated specifically in the pediatric population.

Most strains of enterococci have an MIC to penicillin ≥0.4 μg/mL and an MBC ≥6.25 μg/mL. Therefore, penicillin alone is ineffective and requires the addition of an aminoglycoside to act synergistically to effect a cure. Penicillin plus gentamicin is the preferred initial treatment because of a 20 to 50% resistance (MIC >2000 μg/mL) rate for streptomycin among enterococcal strains.[197] Streptomycin-resistant strains have been shown in vitro to respond to the synergistic effect of penicillin and gentamicin.[198]

Table 90–7. Recommended Antimicrobial Therapy for Infective Endocarditis in Children

Infecting Organism	*Antibiotic Agent*	*Alternate Agent in Allergic Patients*	*Length of Therapy (wks)*
Streptococci			
Susceptible viridans (MIC ≤0.2 μg/mL penicillin G)	Aqueous penicillin G[a] plus streptomycin[b] or gentamicin[c]	Vancomycin[d] plus/minus streptomycin[b] or gentamicin[c]	2–4
Resistant viridans (MIC ≤0.2 μg/mL penicillin G) and enterococci	Aqueous penicillin G[a] plus gentamicin[c]	Vancomycin[d] plus gentamicin[c]	4–6
Staphylococci			
Staph. aureus (methicillin-susceptible)	Nafcillin[e] or methicillin[f] with or without gentamicin[c]	Cephalothin[g] or vancomycin[d]	6–8
Staph. aureus (methicillin-resistant)	Vancomycin[d]	Same	6–8
Staph. epidermidis	Vancomycin[d] with or without rifampin[h]	Same	6–8
Gram-negative organisms			
Enteric bacilli	Ampicillin[i] plus gentamicin[c] (based on in vitro susceptibilities)		6–8
Pseudomonas aeruginosa	Ticarcillin[j] plus gentamicin[c]		6–8
Haemophilus	Ampicillin[i] with or without gentamicin[c]		4–6
Culture-negative			
Postoperative	Vancomycin[d] plus gentamicin[c]		6–8
Nonoperative	Nafcillin[e] or methicillin[f] plus gentamicin[c] with or without aqueous penicillin G[a]		6–8

All daily doses for children with normal renal function are as follows:
[a]Aqueous penicillin G: 200,000–250,000 U/kg, in divided doses q 4–6 hr.
[b]Streptomycin: 20–40 mg/kg, in divided doses q 12 hr.
[c]Gentamicin: 60–90 mg/m^2, in divided doses q 8 hr.
[d]Vancomycin: 40–60 mg/kg, in divided doses q 6 hr.
[e]Nafcillin: 100–200 mg/kg, in divided doses q 4–6 hr.
[f]Methicillin: 100–200 mg/kg, in divided doses q 4–6 hr.
[g]Cephalothin: 100 mg/kg, in divided doses q 6–8 hr.
[h]Rifampin: 15–30 mg/kg, in divided doses q 12 hr.
[i]Ampicillin: 200–300 mg/kg, in divided doses q 6 hr.
[j]Ticarcillin: 200–400 mg/kg, in divided doses q 6 hr.

Once susceptibility to streptomycin is determined, therapy can be adjusted accordingly and should be administered for 4 to 6 weeks.

In patients with IE due to Staph. aureus, a semisynthetic penicillinase-resistant penicillin is given for 6 weeks. Occasionally, a penicillin-susceptible strain (MIC <0.1 μg/mL) is encountered and penicillin G can be used. Although in vitro and animal model studies[199] have demonstrated enhanced killing of these organisms when gentamicin is added to nafcillin, no real value has been found in patients.[200] Therefore, this combination usually is reserved for seriously ill patients. Vancomycin is used in patients allergic to penicillin or in cases where methicillin resistance is encountered.[195] In addition, vancomycin is used in patients with hospital acquired infection due to Staph. epidermidis because of the high rate of methicillin-resistant organisms found in this infection. Bactericidal activity may be increased by the addition of gentamicin or rifampin and is recommended in prosthetic valve endocarditis secondary to Staph. epidermidis.[200]

Infective endocarditis caused by Gram-negative organisms requires individualized therapy based on the findings of in vitro susceptibility testing. When Klebsiella or Pseudomonas is involved, 6 to 8 weeks of therapy with two or more agents may be necessary. In addition, surgical therapy (see below) is frequently necessary. Infections due to Haemophilus sp. usually respond to ampicillin given for 4 weeks, although the addition of an aminoglycoside may improve outcome.[160] Most anaerobes are sensitive to penicillin alone, but when resistant B. fragilis are found, treatment with metronidazole is recommended.

Fungal endocarditis presents the clinician with several difficult problems. The overall survival rate is only 20% and only rarely is medical therapy successful in eradicating the disease. As mentioned previously, delay in diagnosis is frequently encountered because of slow growth in blood culture media. Embolic events frequently are the first serious sign of fungal endocarditis, and may necessitate immediate surgical intervention.[201,202] The primary antifungal agent used is amphotericin B alone or in combination with 5-fluorocytosine. Amphotericin B is given at a dose of 0.5 to 1.0 mg/kg/day. Though usually less severe in children than in adults, toxic reactions may necessitate altering the usual regimen. Fevers, chills, phlebitis, anemia, nephrotoxicity, renal tubular acidosis, hypocalcemia, and thrombocytopenia are the most commonly reported toxic effects. Although the optimal dose of amphotericin B is unknown, total doses of 20 to 50 mg/kg usually are used. Adults should not receive more than 50 mg/day. Therapy usually lasts at least 8 weeks, and evidence of recurrence must be looked for over a long period of time since relapses have been observed up to 2 years after a suspected "cure."[203] Amphotericin B penetrates vegetations poorly and may not prevent continued growth of the fungal organism.[204] Reseeding of the vegetation from distant metastatic sites may occur, further complicating attempts at cure. Most authors agree that the combination of antifungal agents and surgery is the treatment of choice in fungal endocarditis.

In patients with "culture-negative" endocarditis, empiric therapy with two or more agents is employed for 6 weeks, during which time efforts to identify an organism continue. In a study of culture-negative endocarditis in 52 adult patients, survival was correlated with clinical response to the initial choice of antibiotics, with most deaths attributable to congestive heart failure or systemic embolic events.[83]

The use of surgical therapy has been a valuable adjunct to medical therapy of IE in certain circumstances.[205–208] Most studies of the role of surgery have involved adult patients, with the inclusion of some pediatric patients. In a review of 139 patients who underwent surgical therapy for the treatment of IE, the most common reason for referral was congestive heart failure alone or combined with other conditions (i.e., embolization or persistent infection).[209] Aortic valve involvement predominated over mitral valve disease. The early mortality was 25% and the late mortality (>30 days) was 8.6%. Only 1.6% of the patients had residual infection despite the fact that 10% had a positive valve culture at the time of surgery. Jung et al.[210] reviewed the use of early surgical treatment in left-sided disease. The commonest indication for intervention was severe congestive heart failure alone (84%) or combined with other factors (12%). Their early and late mortality rates were 30% and 7%, respectively.[210] They noted that the most significant factor affecting survival was severe cardiac failure, and they emphasize the importance of early intervention. In their cases of fungal endocarditis, recurrent emboli and persistent infection were more common than severe congestive heart failure as the indication for surgery. When considering aortic valve disease alone, unstable hemodynamics may be the primary reason to perform surgery.[211] Placement of a prosthetic valve during active infection seems to contradict classical surgical techniques. However, the incidence of recurrent infection when prosthetic valve replacement is performed in patients other than IV drug abusers is surprisingly low.[166,211] There seems to be no difference in the reinfection rate of bioprosthetic valves as compared with prosthetic valves.[183] Double valve replacement (aortic and mitral) also has been successfully performed when the infection has involved both structures.[183] Extravalvular aortic root infection can also be managed successfully with aortic valve replacement, either alone or with a Teflon patch attached.[166] A recent study by Nihoyannopoulos et al.[212] evaluated surgical therapy in 106 patients at the Hammersmith Hospital in London, England. There were 12 patients with congenital heart disease, including seven with VSD, two with PDA, one with TGA, and two with secundum ASD. The primary indications for intervention were 1) heart failure secondary to valve destruction; 2) removal of a newly leaking prosthetic valve; 3) persistent or recurrent infection; and 4) large left-sided mobile vegetations regardless of the occurrence of embolism. Overall, the patients with congenital heart disease had the lowest mortality. The authors attributed this to the primary involvement of the right side of the heart and the low incidence of embolic events. Mortality was dramatically lower in surgical therapy of prosthetic valve endocarditis than in native valve endocarditis (10% vs 32%). The authors concluded that surgery should be considered earlier 1) when medical treatment is failing, 2) when large mobile vegetations are noted on echocardiographic study, and 3) when fungal endocarditis is encountered. Operative intervention can be performed with good results even during active infection. Patients with infected endocardial pacemaker leads in whom antibiotic therapy fails to sterilize the blood probably need to have these leads replaced and temporary pacing instituted. Permanent pacing leads can be safely placed after successful therapy. Patients who have been successfully treated for endocarditis and who have prosthetic material in the heart should not receive chronic oral "suppressive therapy" in an attempt to prevent a relapse.

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CHAPTER 91

Myocarditis

Richard A Friedman

Myocarditis is an "inflammation of the muscular walls of the heart."[1] In 1984 a group of pathologists meeting in Dallas attempted to define this rather broad term as "a process characterized by inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease."[2] This chapter discusses proven or presumed infectious causes for myocarditis and describes the clinical presentation and etiologies when known.

Myocarditis may be secondary to many of the common infectious illnesses that affect children and infants (Table 91–1), or it may occur as a manifestation of hypersentitivity or as a toxic reaction to drug administration. In general, myocarditis may go unrecognized in a large percentage of patients whose illness resolves spontaneously; in contrast, it may lead to fulminant disease with a rapid progressive downhill course or a chronic state possibly leading to dilated congestive cardiomyopathy.

Early descriptions in the first half of this century classified myocarditis as idiopathic, with histologic findings of diffuse or focal interstitial inflammation. The term *Fiedler myocarditis* has its origins in the description by Fiedler of pathologic changes found in adult patients. He described a diffuse or focal idiopathic or isolated interstitial myocarditis.[3] Myocarditis as a result of rheumatic fever, diphtheria, or other bacterial infection was well recognized although many experts suspected that viruses were also involved in the pathogenesis of the disease.[4]

Myocarditis is a relatively uncommon finding in children, representing only 0.3% of 14,322 patients seen in the cardiology service at Texas Children's Hospital between the years 1954 and 1977. This rate is similar to the findings of a group at the Toronto Children's Hospital between 1951 and 1964.[5] However, not all cases of myocarditis are recognized by the clinician and a much higher incidence is noted in autopsy series. During the same two decades, an autopsy incidence of 1.15% was found at Texas Children's Hospital. This is in contrast to the report by Saphir and colleagues[4] who noted an incidence of 6.83% among 1420 autopsies on children. In Saphir's series nearly one third of the cases were believed to have rheumatic carditis, though this finding was extremely rare in the series from Texas Children's Hospital using histologic examination of the heart (only two patients). One study attempted to estimate the evidence of myocarditis in children who had died suddenly.[6] The control group consisted of children who died a violent death with no history suggestive of myocarditis. They found that 17 of 138 cases (12.3%) revealed evidence of active or healing myocarditis. Fifteen of these cases occurred in the 90 children who died suddenly. In contrast, only 4.2% of 48 children dying a violent death had histologic evidence suggestive of myocarditis. Unfortunately, this was a retrospective study and viral cultures and serologic studies were not routinely obtained at autopsy. In addition, the two groups were not matched for age, sex, or time of death, which may have affected the interpretation. The authors suggested that although further study was needed, the incidence of "silent" myocarditis in children might be higher than expected.

An even greater discrepancy is found in the series by Burch and colleagues,[7] who found evidence of interstitial myocarditis in 29 of 50 infants and young children who underwent routine postmortem examination. Several investigators have found recently that a significant number of patients undergoing endomyocardial biopsy for unexplained myocardial dysfunction had histologic find-

Table 91–1. Etiologic Agents of Myocarditis

Viral
Coxsackievirus A
Coxsackievirus B
Echoviruses
Rubella virus
Measles virus
Adenoviruses
Polio viruses
Vaccinia virus
Mumps virus
Herpes simplex virus
Epstein-Barr virus
Cytomegalovirus
Rhinoviruses
Hepatitis viruses
Arboviruses
Influenza viruses
Varicella virus
Rickettsial
Rickettsia ricketsii
Rickettsia tsutsugamushi
Bacterial
Meningococcus
Klebsiella
Leptospira
Diphtheria
Salmonella
Clostridia
Tuberculosis
Brucella
Legionella pneumophila
Streptococcus
Protozoal
Trypanosoma cruzi
Toxoplasmosis
Amebiasis
Other Parasites
Toxocara canis
Schistosomiasis
Heterophyiasis
Cysticercosis
Echinococcus
Visceral larva migrans
Fungi and Yeasts
Actinomycosis
Coccidioidomycosis
Histoplasmosis
Candida
Toxic
Scorpion
(Diphtheria)
Drugs
Sulfonamides
Phenylbutazone
Cyclophosphamide
Neomercazole
Acetazolamide
Amphotericin B
Indomethacin
Tetracycline
Isoniazid
Methyldopa
Phenytoin
Penicillin
Hypersensitivity/Autoimmune
Rheumatoid arthritis
Rheumatic fever
Ulcerative colitis
Systemic lupus erythematosus
Other
Sarcoidosis
Scleroderma
Idiopathic
Cornstarch

ings suggestive of myocarditis.[8,9] Likewise, patients being investigated for occult ventricular arrhythmias for which no etiology could be proved have also been found to have evidence of interstitial lymphocytic infiltrates suggestive of myocarditis.[10,11] Pomerance and Davies[12] have pointed out the potential for overdiagnosis of myocarditis, noting that about 5% of "normal" hearts may be found to have minor foci of inflammatory cells. They determined that a normal finding was 25–30 interstitial lymphocytes per square millimeter. In addition, the number of lymphocytes per square millimeter in endomyocardial biopsy specimens was less than that found in autopsy specimens (3.5 versus 7.2 cells per square millimeter).

The discrepancy between clinical and autopsy series could be explained by the fact that in a significant number of cases of myocarditis the manifestations may be subclinical and recognized through other findings, such as ECG changes, or perhaps not at all. Myocarditis may also be only one component of a generalized disease; if the cardiac dysfunction is mild, it may be completely overlooked.

EPIDEMIOLOGY

Myocarditis is generally a sporadic disease, although epidemics have been reported. Coxsackievirus B has been the most frequently reported cause of epidemics in children. Geer and Measroch[13] were the first to identify this organism in association with myocarditis, during a nursery epidemic in southern Rhodesia. Other reports from Rhodesia,[14] Holland,[15] the United States,[16] Singapore,[17] and South Africa[18] followed. Infections secondary to coxsackieviruses are common throughout the general population. Target organs include the upper respiratory tract, the gastrointestinal tract, liver (hepatitis), lung (pneumonia), central nervous system (meningoencephalitis), lymph nodes (infectious mononucleosis–like syndrome), the kidney (hemolytic uremic syndrome), and the heart (carditis).[19–21] Significant titers of type-specific protective antibodies are present in most adults in the United States.[21] However, as hygienic and socioeconomic conditions improve, fewer children likely will become infected with this virus. Thus, the potential exists for a greater segment of the adult population to become susceptible to these viral agents later in life.[22] This may become an important problem in pregnant women who, if infected late in pregnancy, may transmit the virus to the fetus in utero or to the neonate. After birth, spread occurs by the fecal/oral or airborne route. The coxsackieviruses B use receptors that are not shared with other enteroviruses to attach to their target cells. It is these receptors that are believed to be essential for viral replication and

may help to determine tissue tropism.[23] Infections owing to the coxsackievirus B or enteroviruses are subclinical in 50% of cases.[21] During an outbreak of coxsackievirus B virus in Europe in 1965, cardiac manifestations were noted in 5% of patients.[24,25] That same year, in similar outbreaks of the disease in Scotland, Finland, and Austria, a much higher incidence of patients (12%) developed some evidence of myocardial dysfunction.[22,23] While myocarditis has been associated with coxsackievirus B serotypes 1–6, the most serious disease has been attributed to types 3 and 4.[16,20,26] Burch et al.[7] demonstrated coxsackievirus B antigens with the use of an immunofluorescent technique in 41% of 29 infants and children who had interstitial myocarditis at routine autopsy. Another study[27] found 1299 cases of unexpected death in an autopsy series of 2427 patients. These authors were able to identify 20 cases of viral myocarditis in this group. Of the 20, nearly half had positive serologic evidence of coxsackievirus B infection. Karjalainen et al.[28] found a 9% incidence of myocarditis in 67 verified cases of influenza infection during a 1978 epidemic in Sweden. Though much less common, coxsackievirus A and echoviruses have also been suspected of causing myocarditis.

Rubella virus, a teratogen during the first trimester of pregnancy, has been implicated in myocarditis. Persistence of the virus in the fetus has been shown to produce severe cases of myocarditis.[29] One study found 10 of 47 infants with congenital rubella to have evidence of myocarditis.[29] Seven of these infants had active disease, and four died with severe myocardial failure. Morbidity secondary to chronic cardiac dysfunction was felt to be severe in the survivors. A significant reduction in the number of cases of congenital rubella has occurred because of aggressive immunization programs, and only 28 cases of rubella myocarditis were recorded in 1975.[30]

Herpes simplex virus infects newborns at a rate of 1 per 7500 deliveries.[31] The types 2 virus is most common and is usually acquired from the mother's genital tract. The wide spectrum of this disease ranges from mild, clinically inapparent disease, to severe fatal encephalopathy. Herpesvirus has been found in the myocardium of autopsy specimens, thus documenting its association with myocarditis.[32]

Osama et al. found a 5.8% incidence of myocarditis in 312 cases of varicella during a one-year period.[33] Patients who complained of skeletal myalgia seemed to have a significantly higher risk of developing cardiac involvement.

PATHOLOGY

Immunology

The microscopic and immunologic changes seen in patients with viral myocarditis have been well described. However, to examine the immunopathogenesis of this disease, it has been necessary to use animal models, the most thoroughly studied of which has been the murine model. Coxsackievirus B and encephalomyocarditis viruses have been extensively studied.

It has been demonstrated that between 24 and 72 hours after infection with coxsackievirus B, a viremia exists, with maximum growth in the tissues between 72 and 96 hours.[34] Shortly thereafter, virus titers decline; essentially no organisms can be found by 7 to 10 days after inoculation.[23] As virus titers decline, antibody concentrations increase, implying that antibody has an active role in viral clearance.[35] Macrophages appear 5 to 10 days after infection in the coxsackievirus B model of myocarditis.[23,36]

Factors that have been shown to affect the severity of myocarditis in the murine model include age, strain of mouse, viral variant, and gender of the host.[37] Several mechanisms have been shown to be active in the production of myocarditis in this model. Viruses have been shown to be directly associated with myofiber destruction.[38–40] However, the greatest degree of damage is probably due to an interaction between the myofiber and T cells. Viral-induced changes of the myocardial cell produce a neoantigen that is recognized by cytotoxic T lymphocytes, which preferentially destroy the myocardial cell. In addition, coxsackievirus may induce cytotoxic T lymphocytes that are autoreactive against antigens on infected myocytes. Mice who are pretreated with antithymocyte serum and thus lack a normal immunologic response develop a less extensive myocardial necrosis when compared with animals similarly infected and treated with normal rabbit serum.[23] Animals who are deficient in T cells clear their viremia normally, but develop a significantly lesser degree of myocardial injury. The implication is that the T cells are not required in elimination of virus, but play a delayed role in the major inflammatory response.[23,40] Mice who are pretreated with neutralizing antibody fail to develop myocarditis,[32,41–43] which implies that a combination of macrophages and antibody suppresses viral infection.

Another type of cell—the natural killer (NK) cell—is important in the pathogenesis of myocarditis. Animals who are depleted of their NK cells prior to infection with coxsackievirus have been shown to develop a more severe myocarditis. One study[44] used murine skin fibroblasts to demonstrate the antiviral activity of activated NK cells. Natural killer cells are activated by interferon, which is an indirect modulator of myocardial injury. Murine skin fibroblasts served as target cells for coxsackievirus B–sensitized cytotoxic T cells. The NK cells were shown to specifically limit the nonenveloped virus infection by killing the virally infected cells. This finding has important implications in host immunity and may help to explain why female mice develop a less severe myocarditis than males. Male mice have been shown to be much less efficient in activating NK cells, which, as mentioned above, are directly responsible for viral clearance. Presumably, the more efficient viral clearance is, the less is the opportunity for viral-induced neoantigen production and recognition by cytotoxic T lymphocytes.

Woodruff has elucidated the different ways that T cells can effect injury.[23] They include accumulation of activated macrophages, production of antibody and antibody-dependent cell-mediated cytotoxicity, direct lysis by antibody and complement, and direct action of cytotoxic T cells. The primary importance of cytotoxic T cells in direct myocardial cell injury was demonstrated in BALB/c mice infected with coxsackievirus B3.[40] Both virus-infected and noninfected myocytes were destroyed in T cell–deficient animals. The infected host cells were thought to stimulate the production of a subset of cytotoxic T cells responsible for the injury. These cells then recognize virus-specific and major histocompatibility antigens (modified H_2 antigens) present on the cell surface and directly interact, resulting in myocytolysis. This ongoing injury has been considered an autoimmune-type process.[23,40] In support of this concept, Pacque et al.[45] infected the CD1 mouse with coxsackievirus B3 and demonstrated in the hearts of mice previosly infected with this virus a KCl extractable antigen

that was specifically immunoreactive with immune mouse peritoneal exudate cells (i.e., that stimulated production of a migration inhibitory factor). The authors were unable to demonstrate viral activity in animals who had this extractable antigen. In addition, antigen responsible for cytotoxic T-cell activity cannot be detected by using antiserum containing antibodies directed at the structural components of the viral capsid. The ineffectiveness of antiviral serum in preventing myocarditis has also been demonstrated.[46]

Lyden et al.[47] studied the susceptibility variation of the BALB/c mouse to coxsackievirus B3. The age of greatest susceptibility was between 16 and 18 weeks, with males having a maximal rate of myocarditis greater than that seen in females. Enhanced myocarditis seen in older females was eliminated when they were treated with estradiol, implying that sex hormones play a key role in host susceptibility. In vitro and in vivo studies have shown that testosterone seems to increase the cytolytic activity in males preferentially over females. Either a preferential stimulation of T helper cells or an inadequate stimulation of T cytolytic/suppressor cells could explain why antibody responses to various antigens may frequently be enhanced and cellular immune responses depressed in females. Huber and Lodge[48] demonstrated that host genetic composition not only affects the severity of disease, but also plays a role in the pathogenic mechanisms involved. Important differences were found when coxsackievirus B3 was used to induce myocarditis in the BALB/c mouse and the DBA/2 mouse. The BALB/c mouse developed myocarditis in response to cytolytic T cells. Two distinct cytolytic T cell populations are formed in the BALB/c mouse: one recognizing virus-infected cells and producing direct myocytolysis, and another that destroys uninfected myocytes and is believed to be an autoreactive lymphocyte. Complement depletion increased the amount of inflammation in this species, and no reactive immunoglobin G antibody was found in the myocytes. In contrast, in the DBA/2 mouse it was the T helper cells that indirectly mediated the course of disease, and complement depletion reduced inflammation in this species. Cytolytic T cells are produced, but apparently are not pathogenic and immunoglobin G antibody is found in the myocytes.

Several other viral agents have been used to produce experimental myocarditis. Sakamoto et al.[49] produced myocarditis using influenza A virus (H2 N2) in mice. Mice who were pretreated with radiation or depleted of T lymphocytes did not develop disease. Encephalomyocarditis virus (ECM) has been used to develop models of acute and chronic myocarditis in mice. This virus is a picornavirus, similar to the coxsackievirus group. Studies have demonstrated a progression from acute myocarditis to dilated cardiomyopathy similar to that seen in human beings.[41,50]

Several studies have been done in human beings as well. Maisch et al.[51] demonstrated antibody-mediated cytolysis in 30% of 144 patients with suspected myocarditis as well as in 18 of 19 patients with proven viral infections due to coxsackievirus B, influenza A, or mumps. A muscle-specific antimyolemmal antibody (AMLA) was found in these patients and correlated with the degree of in vitro induced cytolysis of rat cardiocytes. Bowles et al.[52] used complementary DNA (to coxsackievirus B2 RNA) cloning techniques and developed a coxsackievirus B–specific cDNA "hybridization probe" that detected virus nucleic acid sequences in patients diagnosed as having active or healed myocarditis or dilated cardiomyopathy. As a control they used patients with unrelated disorders and found no virus-specific sequences in those patients. This suggested that in patients with congestive cardiomyopathy or healing myocarditis, viral particles persist even though viral culture is almost always negative. The findings imply a continual viral replication in cells, which may conceal the antigenicity by an immunologic process that prevents correct posttranslational processing of capsid proteins.[52] Hori et al. found adult patients with myocarditis to have been exposed to a greater number of coxsackievirus B1–6, as demonstrated by the number of positive and negative responses to neutralizing antibodies of those viruses.[53] These authors believed that immunization against several types of coxsackievirus B was essential in the development of myocarditis. Although they postulated this "cross immunization" theory, a few cases of myocarditis in their patients involved exposure to only one type of coxsackievirus B, shedding doubt on the validity of their theories.

A defect in cell-mediated immunity as expressed in a reduction in concanavalin A–induced suppressor cell activity has been demonstrated in patients with myocarditis and dilated cardiomyopathy as compared with healthy controls.[54]

In summary, the pathogenesis of myocarditis can be viewed as follows (Fig. 91–1). Infection of the mouse with coxsackievirus B3 induces a viremia and replication of this virus within the myocardial cells. Direct viral myocytolysis ensues, with production in other cells of neoantigen in response to viral infection. Cytotoxic T cells directed at both infected and noninfected (autoimmune) cells produce further injury. Natural killer cells attack the virally infected cells only and are responsible for viral clearance. Antibody binding and complement-mediated cell destruction also occurs in the delayed immunologic response. Host factors, including age, sex, and immunocompetence, play key roles in modulating these processes.

Gross and Microscopic Findings

The pathologic findings are usually nonspecific, with similar gross and microscopic changes noted irrespective of the causative agent.[3,4,55–59] Grossly, the weight of the heart is increased; all four chambers are affected. The muscle appears flabby and pale with petechial hemorrhages often seen on the epicardial surfaces, especially in cases of coxsackievirus B infection. A bloody pericardial effusion may also be seen relating to the often combined finding of pericarditis. The ventricular wall is frequently thin, though hypertrophy may be found as well. Usually the valves and endocardium are not involved, although they may be glistening white in cases of chronic myocarditis. This finding has suggested to some investigators that the disease process known as endocardial fibroelastosis, which may present with similar clinical findings, could represent an end result of viral myocarditis, possibly induced in utero.[60,61] Hutchins and Vie[61] studied the hearts of 64 children with a diagnosis of myocarditis or endocardial fibroelastosis. They found that 41 patients had features shared by both diseases, 18 had endocardial fibroelastosis only, and 5 had myocarditis only. A history of acute illness (disease onset to death 2 weeks or less) was found only in the patients with myocarditis. In the 41 patients in whom features of both diseases existed, the time from onset of disease to death was between 2 weeks and 4 months, while in cases of endocardial fibroelastosis the onset of disease to death was greater than 4 months. Support for this observation was reported by Hastreiter and Miller,[60] who found microscopic evidence

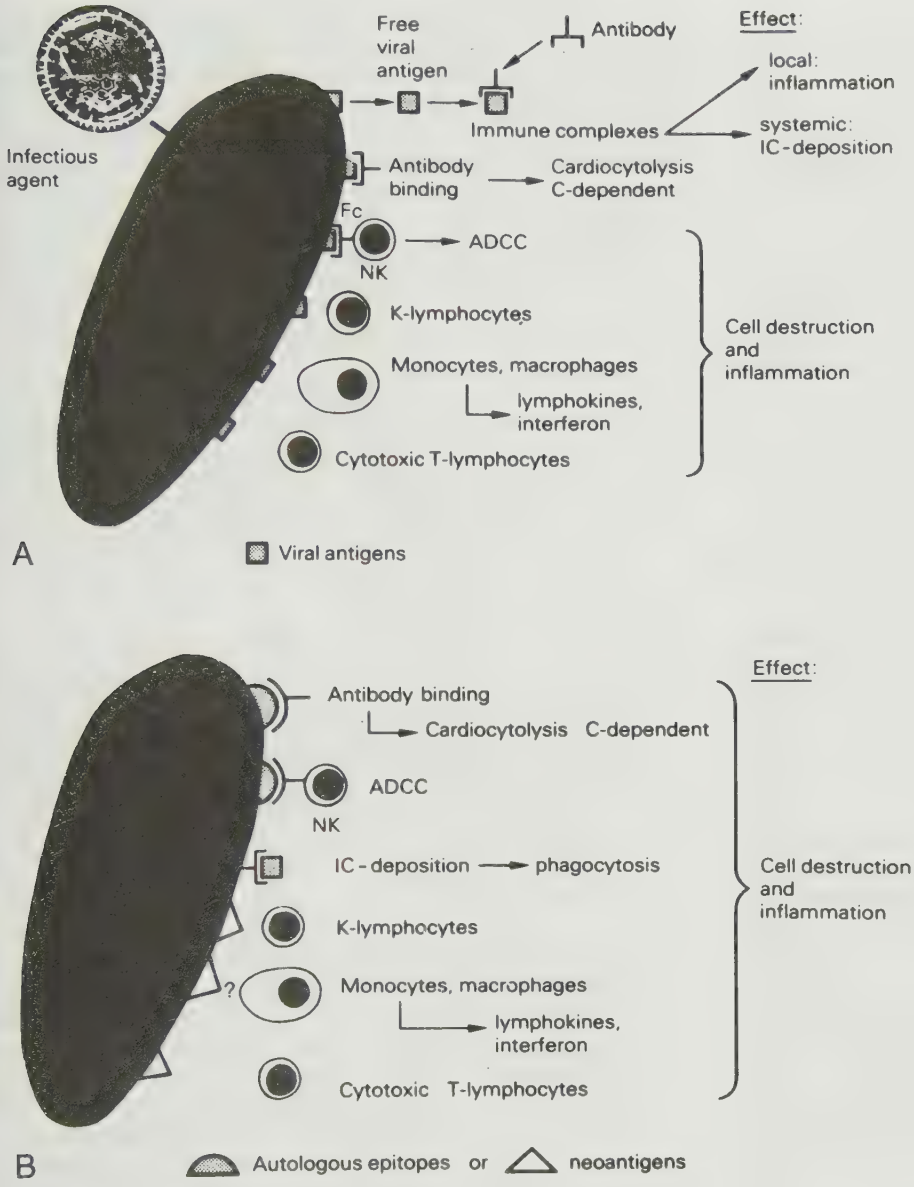

Fig. 91–1. (A) Early immunopathogeneis. The cell cycle is altered by viral infection. Viral proteins are expressed on the surface of the cell and become targets of various immunologic effectors. These include the monocytes and macrophages, which release mediators; cytotoxic T lymphocytes and K cells, which lyse the myocardial cell; and NK-cells, which together with antibodies also effect cell lysis. Complement-activated antibody-mediated cell destruction also occurs, with the production of antiviral antibodies. Formation of immune complexes may occur when circulating viral antigen is coupled to viral antibodies, resulting in local or systemic reactions. (B) Delayed immunopathogenesis. In addition to the mechanisms described in (A), modulation of the inflammatory response by T cells (helper and suppressor types) against autologous heart cells occurs. Complement-activated antibody-mediated cell destruction is more important than antibody-dependent cellular cytotoxicity (ADCC) in this phase of the injury process. The presence of viral antigens during this phase is negligible compared with the level present during the early phase of injury.

of myocarditis after transthoracic needle biopsy in a child who had the classical clinical picture of endocardial fibroelastosis.

Fruhling et al.[62] demonstrated coxsackievirus B3 in the myocardium of 13 of 28 infants with endocardial fibroelastosis, and Van Reken et al.[63] found echovirus 9 in a 5-month-old infant with myocarditis and severe congestive heart failure who also had histologic findings consistent with endocardial fibroelastosis. In addition to isolating virus in the heart and lungs, the liver and lymph nodes were also involved in the latter case.

Mural thrombi have been described in the left ventricles of some patients with myocarditis as well as small emboli in the coronary and cerebral vessels.[64] Coronary emboli, though rare, may produce areas of ischemia and/or injury with resultant production of the cardiac arrhythmias that sometimes occur during the acute disease.

The typical microscopic picture of acute myocarditis is that of a focal or diffuse interstitial collection of mononuclear cells, including lymphocytes, plasma cells, and eosinophils. Polymorphonuclear types are only rarely noted, except in cases of bacterial myocarditis. As mentioned previously, viral particles are rarely recognized on electronmicroscopic investigations.[59,65]

Extensive necrosis of the myocardium, with loss of cross striation in the muscle fibers and edema, is seen in severe infections, but especially with coxsackievirus. Perivascular accumulation of lymphocytes and plasma cells has been described with coxsackievirus B myocarditis but is usually a minor finding. In disease due to rickettsiae,[56] varicella,[66,67] trypanosomes,[68,69] or other parasites,[70] and in reactions to sulfonamides,[71] this is a much more prominent finding.

Myocarditis secondary to diphtheria infection is frequently complicated by arrhythmias, especially complete atrioventricular block. Diphtheria exotoxin has a particular affinity for conductive tissue. It interferes with protein synthesis by inhibiting a translocating enzyme in the delivery of amino acids. Triglyceride accumulation occurs as a result of induction of abnormal carnitine metabolism, and fatty changes of the myofibers are seen.[72]

Myocarditis due to bacterial agents usually presents a different

picture than that seen with disease due to viral agents. Microabscesses and patchy focal suppurative changes may be seen.[72] A combined perimyocarditis is also frequently encountered.

Trichinella species usually cause a focal infiltrate with lymphocytes and eosinophils. Larvae are usually not identified.

A severe myocarditis may develop in response to Trypanosoma cruzi, with the development of Chagas' disease. This disease, which is uncommon in North America, can affect up to 50% of the population in an endemic region, such as South America. Protracted heart failure and death may ensue after acute infection. Microscopic examination demonstrates the presence of the organism as well as neutrophils, lymphocytes, macrophages, and eosinophils.[72]

Sudden infant death syndrome occurs in up to 1 in 500 children and could be due to cardiac arrhythmias that may result from myocardial inflammation.[73] James[74] described a resorptive, degenerative process in the His bundle and left margin of the atrioventricular node with the absence of inflammatory cells in cases he studied of infants who died in northern Ireland. He concluded that lethal arrhythmias or conduction disturbances could be due to developmental histologic changes in these critical regions of the heart. Jankus[75] demonstrated lymphocytic infiltrates in the region of the His bundle and left fascicle in a 3-month-old child who died suddenly. However, no degenerative changes were seen and thus the significance of these findings remains speculative.

Giant cell myocarditis is diagnosed when giant cells are found with or without granulomas. Patients with tuberculosis, syphilis, rheumatoid arthritis, rheumatic heart disease, sarcoidosis, and certain fungal or parasitic infections may have granulomas within the myocardium. Giant cells were also described in so-called idiopathic or Fiedler's myocarditis. In a significant number of cases, however, giant cells are found but no specific cause is discovered. There appear to be two types of giant cells, one of which is myogenic in origin and thought to represent a transitional form of myocardial cells. Granulomas are usually not found with these types of cells. The more characteristic type of giant cell is probably derived from interstitial histiocytes and is usually found in patients with myocarditis not due to viral agents. Similar cells were noted in an adult who had received neomercazole therapy,[56] and there has been a report of granulomatous myocarditis associated with phenylbutazone ingestion.[76]

PATHOPHYSIOLOGY

Myocardial function is usually reduced in the presence of extensive interstitial inflammation or injury, resulting in cardiac enlargement and an increase in the end diastolic volume. Normally, this increase in volume results in an increased force of contraction, ejection fraction, and cardiac output, as described by the Starling mechanism. However, in the disease state, a reduced cardiac output results from the inability of the heart muscle to respond to these stimuli. Interactions with the sympathetic nervous system may preserve systemic blood flow secondary to vasoconstriction and increased afterload. Congestive heart failure usually ensues with disease progression or with intercurrent infections that cause fever or anemia, which further stress the myocardial reserve. The progressive increase in end diastolic volume and pressure results in increasing left atrial pressure, which is transmitted into the pulmonary venous system. The resulting increasing hydrostatic forces overcome the colloid osmotic pressure that normally prevents transudation of fluid across the capillary membranes. The typical picture of congestive heart failure with pulmonary edema and systemic venous engorgement is common in the more acute forms of myocarditis. In some infants and children the initial presentation is that of right heart failure.[77] Echocardiographic examination may demonstrate severe left ventricular dilation during diastole and systole and a decrease in ejection fraction usually can be noted. Evaluation of ventricular function using M-mode echocardiography is useful in the acute setting as well as to assess function during therapeutic intervention. Gutgesell and colleagues have established normal echocardiographic standards for children.[78]

During the healing stages of myocarditis, fibroblasts replace normal myofibers, with resultant scar tissue formation. Reduced elasticity and ventricular performance can result in a picture of continuing congestive heart failure. Attempts to preserve cardiac output may exacerbate ischemia, with sinus tachycardia further worsening the supply/demand ratio for oxygen in the heart muscle.

CLINICAL PRESENTATION

The clinical presentation of myocarditis varies considerably in response to various host factors, including age, gender, and immunocompetence. One end of the spectrum results in a fulminant and rapidly fatal illness; at the other end, the majority of cases probably go unnoticed with no apparent clinical illness. Newborn infants are very susceptible to infection with coxsackievirus B, which could result in the severe form of the disease.[15,16] In addition, infections with rubella,[29] herpes simplex,[32] and toxoplasmosis[56,68] may also result in a severe form of illness in infants.

As previously mentioned, myocarditis may be but one component of a more severe generalized illness with concomitant hepatitis and/or encephalitis.[16,26] The myocarditis may be only a mild clinical disturbance in these cases.[79,80] Brightman et al., during a virologic survey in their institution, found a nursery epidemic of coxsackievirus B5 infection in preterm infants. The disease was clinically unnoticed and discovered only by chance during this survey. No instances of severe myocarditis were seen; all infants recovered fully from their infection. The major symptoms were lethargy, failure to gain weight, and aseptic meningitis. In a review of 25 infants with myocarditis due to coxsackievirus B, other symptoms of lethargy and anorexia heralded the onset of severe disease, highlighting the importance of careful attention to any symptom in the newborn no matter how nonspecific.[16] Fever was recorded in over 50% of the cases in this study, although hypothermia was also noted. Cyanosis; respiratory distress; and/or tachycardia, cardiomegaly, or ECG changes were present in 19 of 23 infants; vomiting was noted in 4.

Clinical manifestations of myocarditis are generally less severe in older infants and children than in newborns.[4,77,81–84] Rapidly fatal illness has been reported in association with myocarditis of unknown etiology,[85] enteroviruses,[86] adenoviruses,[87] mumps,[88] varicella,[66] cytomegalovirus,[89] and diphtheria.[90] The usual clinical picture is either an acute or subacute illness often beginning with a mild respiratory infection and low-grade fever.[91] Initial symptoms in infants include irritability and periodic episodes of pallor, which may precede the sudden onset of cardiorespiratory symptoms. Some children may complain of abdominal pain.[83] The physical examination usually shows the child to be anxious and apprehensive, though some appear apathetic and listless. Pallor and mild

cyanosis may be present; the skin may be cool to touch and mottled appearing. Respirations are usually rapid and sometimes labored; grunting may be prominent. The pulse is thready, although blood pressure may be normal or slightly reduced unless the patient is in shock. Palpation of the chest demonstrates a quiet precordium. Tachycardia is usually present. The heart sounds may be muffled, especially in the presence of pericarditis, and a gallop rhythm is frequently heard. A soft first sound at the apex was found to be the most sensitive clinical sign of myocarditis in one study.[92] It should be noted, however, that a soft first heart sound without evidence of myocarditis may be secondary to a prolonged PR segment seen during many febrile illnesses.[93] With severe ventricular dysfunction, mitral regurgitation may be heard with a pansystolic murmur at the apex. Auscultation of the lungs reveals scattered rhonchi and fine crepitations in the lung bases. Although peripheral edema is rare, hepatomegaly is almost uniformly found. Some infants may have only mild congestive heart failure without evidence of peripheral circulatory compromise, while others have such a mild illness that the only abnormal finding may be a conduction disturbance on the surface electrocardiogram.

DIAGNOSIS

The diagnosis of myocarditis is often difficult to establish but should be suspected in any infant or child who presents with unexplained congestive heart failure. The common occurrence of fever in children clouds the history of a recent viral illness, but if a viral illness is documented in the recent past it should heighten suspicion for the diagnosis.

Electrocardiogram

A sinus tachycardia out of proportion to the level of fever in association with a quiet precordium and a gallop rhythm should strongly suggest the diagnosis. A third heart sound—a common finding in normal healthy children—is usually associated with a relatively hyperdynamic precordium with heart sounds that are increased or crisp. When a prominent third heart sound exists without these findings a significant disturbance in ventricular compliance is usually present and deserves further investigation with a chest film, electrocardiogram, and echocardiogram. Children with myocarditis and congestive heart failure usually have cardiomegaly and pulmonary edema visible on their chest radiograph.

In newborn infants whose first sign of illness may be acute circulatory collapse, the cardiac size may be normal. This may also be true in children who present with an arrhythmia secondary to myocarditis. Stokes-Adams attacks secondary to complete atrioventricular block may also be a presenting sign in myocarditis in children.[94]

When an arrhythmia occurs following a febrile illness, the clinician should be suspicious of the diagnosis and look for other signs of disease.[95,96] One study found significant arrhythmias in five infants with isolated myocarditis.[85] Four of the five infants died, and three of them had paroxysmal atrial tachycardia. Other reports of paroxysmal atrial tachycardia have been reported in patients with viral myocarditis[95,96] as well as in patients with disease due to diphtheria.[90] Atrial ectopic focus tachycardia may mimic sinus tachycardia and should be suspected in a patient with persistent sinus tachycardia and cardiomegaly. Careful inspection of the P wave axis and morphology in a 15-lead electrocardiogram, as well as use of a 24-hour Holter monitor to observe the variance in rate, is essential in helping to establish the diagnosis of myocarditis. Complete atrioventricular block secondary to idiopathic myocarditis,[94,97] rubella.[98,99] coxsackievirus,[100] and respiratory syncytial virus[101,102] has been described. Some of these patients developed permanent atrioventricular block[98,100,101] and required permanent pacing, while in others it was noted to be a transitory finding.[97,102]

The classically described electrocardiographic pattern in myocarditis is that of low-voltage QRS complexes (less than 5 mm total amplitude in all limb leads) with low amplitude or slightly inverted T waves and a small or absent Q wave in leads V_5 and V_6. The low voltage may also be present in the precordial leads.

Karjalainen examined the electrocardiograms of 87 patients, 28 of whom had myocarditis.[103] He found that the most frequent finding was that of T-wave changes consisting of reduced amplitude or inversion in the left chest leads. Sinus tachycardia was the most common arrhythmia, followed by uniform PVCs. Another study[104] described four patterns of ECGs in patients with proven viral myocarditis: 1) normalization even in the presence of severe myocardial damage during the acute stage, 2) ''pseudoinfarction'' patterns with pathologic appearing Q waves and poor R wave progression in the precordial leads, 3) conduction disturbances possibly requiring pacemaker support, and 4) chronic arrhythmias consisting of ventricular tachycardia and supraventricular tachycardia.

The electrophysiologic effects of myocarditis have also been studied in animals. In one study coxsackievirus B3 myocarditis was produced in hamsters.[105] The authors found ST- and/or T-wave changes on the surface ECG in 80% of the animals. The peak changes were seen between days 2 and 4, when mortality was highest. Histologic examination revealed that the inner third of the endocardium was primarily involved, suggesting that subendocardial injury corresponded to the ST- and T-wave changes found on the surface electrocardiogram. In another study, myocarditis was induced in DBA/2 mice with encephalomyocarditis virus.[106] Advanced atrioventricular block, premature atrial contractions, and premature ventricular contractions were all seen acutely. The chronic stage was characterized by sinus tachycardia and low voltage of the QRS complex. In the late chronic stages, QRS voltages returned toward normal, possibly reflecting diminished myocardial edema and/or compensatory ventricular hypertrophy.

ST segment and T-wave changes are sensitive indices of myocardial ischemia; however, they also appear to be nonspecific findings. This is true of the prolongation in the PR segment, as is evidenced by its common occurrence during fever. Scott and colleagues[93] found a 1.49% prevalence of these findings in a group of 737 infants and children with concurrent respiratory tract infections, a finding similar to their control group. Another study demonstrated PR-segment prolongation and T-wave changes in infants and children with pneumonia and no signs of myocarditis.[107] Another nonspecific finding—prolongation of the QT interval—has been noted in acute myocarditis as well as in measles and poliomyelitis[108,109] without myocardial involvement.

Echocardiogram

As mentioned previously, the echocardiogram is essential in helping to establish the diagnosis. Pericardial effusion as a cause

of cardiomegaly can be easily ruled out with either single crystal or 2-D techniques. Depressed ventricular function with dilation of one or more chambers, in the absence of any structural abnormality, helps to establish the diagnosis.

Endomyocardial Biopsy

Magnetic resonance imaging has recently been advocated as a possible screening test to help diagnose myocarditis. Screening of patients with dilated cardiomyopathy using gallium 67 may help to select a subgroup of patients who could benefit from endomyocardial biopsy. The biopsy would then be used to confirm the presence of active inflammation and may aid in tailoring therapy. In one study, 68 patients with a diagnosis of dilated cardiomyopathy underwent 71 parallel studies with gallium 67 scanning and endomyocardial biopsy. A dense gallium uptake was found in 5 of 6 patients whose biopsy samples showed active inflammation. Only 9 of 65 negative biopsies had equivocally positive scans. This translated into a 36% incidence of myocarditis on biopsy with positive scan, versus only a 1.8% incidence of myocarditis on the biopsies with negative scans.[110] This technique has not been used in children yet, but may prove to be a relatively safe and effective method in helping to select children for biopsy.

Cardiac catheterization is probably unnecessary in most cases of myocarditis and potentially dangerous in all patients; if it is performed, acutely ill patients should be stabilized before undergoing the procedure. Infants require study to exclude anomalous origin of the left coronary artery, although recent advances in echocardiography have helped to establish or rule out this diagnosis.

During the past decade endomyocardial biopsy has become a relatively safe and effective means of sampling heart muscle. This technique was introduced in 1962 by Sakakibara and Konno,[111] but did not gain wide acceptance in the United States until 10 years later. The widest application for endomyocardial biopsy is in adult patients as well as pediatric patients who have undergone cardiac transplantation in an attempt to assess the degree of allograft rejection.

The major usefulness of endomyocardial biopsy is to help establish the diagnosis of myocarditis and possibly classify the phase of disease (acute, healed, or chronic). Histologic classification has proved to be difficult and at times controversial. The method of sampling small areas may preclude accurate diagnosis, especially if the disease is focal. In the majority of patients, multiple samples (at least three) are obtained from the right ventricular septum and/or apex. Some authors believe sampling from other areas of the heart, such as the left ventricle, to be more sensitive,[112] but this technique has not been widely applied. A recent study[113] reported the findings of normal myocardium examined with hematoxylin and eosin stain as compared to staining with monoclonal antibodies. These findings supported the data of Edwards et al.[114] who found less than five lymphocytes per high-power field (400×). There was no correlation between the peripheral lymphocyte count and the count of lymphocytes in the myocardium. Specifically, B cells and killer T cells (NK cells) were uncommon, whereas the helper-type T cell (OKT4) predominated over the suppressor/cytotoxic type of T cell (OKT8) in a ratio similar to that found in the peripheral circulation (1:44). Other authors[2,4] have pointed out that endomyocardial biopsy may miss focal inflammation in cases of suspected myocarditis and that a thorough examination of the myocardium (i.e., obtaining as many biopsy specimens as possible) should be performed to get a true estimate of whether a disease process exists.

A major problem with endomyocardial biopsy has been overinterpretation or misinterpretation of the biopsy specimen. Investigators have stressed the importance of complete investigation of biopsy samples because of the confusion between findings in patients with idiopathic dilated cardiomyopathy and those with active myocarditis. In one study, 87% of patients with dilated cardiomyopathy had leukocytic infiltrates.[115] Immunocytochemical techniques using monoclonal antibodies may be a more specific way of investigating biopsy samples.[116] A wide variety of lymphocytes are found within the myocardium. They include the OKT4 (helper/inducer), the OKT8 (suppressor/cytotoxic), the OKT11 (pan T cell), the beta-1 lymphocyte, the natural killer cell, the T200 (panleukocyte), and the macrophage monocyte cells. One study examined endomyocardial biopsies of 80 adult and pediatric patients, 57% of whom had a prebiopsy diagnosis of dilated cardiomyopathy and 29% of whom had a prebiopsy diagnosis of myocarditis.[116] Histologic examination showed that 45% of the patients were normal, 3% had active myocarditis, 4% had borderline myocarditis, 6% had dilated cardiomyopathy, and the remainder had nonspecific or nondiagnostic findings. Immunocytochemical studies were then performed utilizing the panleukocyte marker. These studies correlated with findings from the hematoxylin and eosin stain. They also correlated with the sum of the OKT11, beta-1, NK, and macrocyte monophage cells. In 16 patients thought not to have myocarditis based on findings from examination of tissue stained with hematoxylin and eosin, the immunoperoxidase-positive cells were found to be T lymphocytes of the OKT11 type and monocyte macrophages. However, in the patients with active myocarditis, the largest population of cells was that of the OKT8 type. Those patients also had an abnormal OKT4/OKT8 ratio. These newer techniques will probably be used more frequently in the future and will help to determine specifically the type of lymphocytic infiltrate present in any case.[116]

Recent studies[9,10,117] have employed endomyocardial biopsy to investigate patients who present with occult ventricular arrhythmias and a clinical picture of dilated cardiomyopathy. The establishment of a diagnosis helped tailor therapy with improvement of the arrhythmias in some patients.

Fenoglio and colleagues[118] used endomyocardial biopsy to establish the diagnosis of myocarditis in 34 patients who presented with dilated cardiomyopathy. Classification of these patients on the basis of clinical and histologic findings was performed in an attempt to stratify patients who might benefit from immunosuppressive therapy. Three groups—acute, rapidly progressive, and chronic—were formed and it was found that immunosuppressive therapy was beneficial only in the chronic patients. More recently, Dec et al. studied 27 patients referred for endomyocardial biopsy with the diagnosis of dilated cardiomyopathy.[119] Though two thirds of the patients had a biopsy consistent with myocarditis, there seemed to be no correlation between histologic classification and outcome. More importantly, there was no difference in outcomes between the group receiving immunosuppressive therapy and the group who did not receive these drugs. The biopsy was negative in 30% of the patients in this study who had clinical criteria of myocarditis and was positive in two of five patients without any clinical evidence of myocarditis.[119]

Olsen[120] reviewed 1200 biopsy specimens from patients with a clinical diagnosis of dilated cardiomyopathy and found that approximately 25% had a diagnosis of myocarditis based on critical evaluation of their tissue specimens. Unfortunately, there are no large series of pediatric patients with myocarditis to help clarify this issue.

Most authors agree that in the vast majority of patients with idiopathic dilated cardiomyopathy it is probably the result of previous viral myocarditis. Thus, the present interest in using endomyocardial biopsy technique to help establish a subset of patients with active disease who would benefit from some type of therapy not yet elucidated has some validity.

Laboratory Tests

Though rarely successful, an attempt should be made in each child with the suspected diagnosis of myocarditis to identify the offending organism.[121–125] Early in the course of illness it is possible to isolate the virus from the stool, throat washings, or, rarely, the blood. Active infection is diagnosed when a fourfold increase is found in antibody titer to the virus.

Criteria that would help establish a diagnosis of coxsackievirus myocarditis have been suggested.[36] Two high-order associations were identified: 1) isolation of the virus from the myocardium or pericardial fluid, and 2) localization of type-specific virus in the myocardium, endocardium, or pericardium at sites of pathologic change. Moderate-order associations were present 1) if the virus was isolated from the pharynx or stool and a four-fold increase in type-specific neutralizing, hemagglutination-inhibiting, or complement-fixing antibodies was demonstrated, or 2) if viruses isolated from the pharynx or stool with a concurrent serum titer of 1:32 or greater of type-specific IgM neutralizing or hemagglutination-inhibiting antibodies.

IgM-specific antibody titers to coxsackieviruses B1, 3, 4, 5, and 6 may be identified and are useful in helping to estabish the diagnosis.[124] Antigens in the myocardium may be identified using immunofluorescent techniques.[6] In the chronic state, viral identification is usually unsuccessful.[24]

Though a diagnosis of myocarditis is being entertained, blood cultures should be obtained in any infant with fever and signs of compromised cardiovascular function. A complete blood count should be performed, and a leukemoid reaction may be noted.[126] The erythrocyte sedimentation rate is usually elevated during acute myocarditis, although a normal value does not exclude the diagnosis. Elevated levels of serum glutamic–oxaloacetic and glutamic–pyruvic transaminase can occur and be the result of a generalized viral infection, though they may also be seen during episodes of diphtheritic myocarditis.[127] Creatine phosphokinase and lactate dehydrogenase enzymes should also be measured. One study found that elevations of isozyme 1 of LDH were a specific finding in patients with idiopathic myocarditis.[128]

Differential Diagnosis

Any cause of acute circulatory failure may mimic the presentation of acute myocarditis. Hypoxia, hypoglycemia, and hypocalcemia in newborns may accompany heart failure. Circulatory collapse with shock frequently occurs in cases of overwhelming sepsis in this age group. Serum measurements of glucose and calcium as well as blood cultures if sepsis is suspected should be obtained in infants presenting with heart failure.

Many infants with significant structural defects of the heart (e.g., hypoplastic left heart syndrome, critical aortic valve stenosis) may have no audible murmur when severely ill because of extremely low cardiac output. When cardiac function is improved, however, murmurs as well as a hyperactive precordium and clear, rather than muffled, heart sounds may be apparent. In the evaluation of such patients, echocardiographic diagnosis is essential to rule out structural abnormalities.

Beyond the immediate neonatal period, many other causes of myocarditis are possible. Anomalous left coronary artery arising from the pulmonary artery should be ruled out with echocardiographic or angiographic investigation. Endocardial fibroelastosis, Cori type II glycogen storage disease (Pompe's disease), medial necrosis of the coronary arteries, and left atrial myxoma[129] are among the many diseases that can present with symptoms suggestive of myocarditis. Murmurs may be audible with anomalous left coronary artery or endocardial fibroelastosis. They are usually apical in location, rarely more than grade 3/6, and usually secondary to mitral insufficiency. Endocardial fibroelastosis is impossible to differentiate from myocarditis by clinical presentation alone. Endomyocardial biopsy and angiographic changes of the left ventricle will help to make the diagnosis. The ECG in anomalous left coronary artery may show a pattern of myocardial infarction, with abnormal Q waves in the anterolateral precordial leads. A QR pattern with inverted T waves in limb leads I and aV_L may also be noted.

Pericarditis, which may be secondary to viral illness, occurs in children rather than in infants. The clinical history may be similar to patients with myocarditis. Cardiovascular function, however, is usually less severely compromised for the degree of apparent cardiomegaly owing to the amount of pericardial effusion. Cardiac tamponade may occur in severe cases and may present with circulatory collapse. Pericarditis may coexist with myocarditis—so-called perimyocarditis—and a clinical picture consistent with both diseases may be found. An echocardiogram is essential in establishing whether a pericardial effusion is present as well as to establish left ventricular size and function. Perimyocarditis may be seen with rheumatic fever, collagen vascular, and other autoimmune diseases, as well as with coxsackievirus B disease. Myocarditis has been described with rheumatoid arthritis.[130] systemic lupus erythematosus,[131] and ulcerative colitis.[132]

TREATMENT

Care of a patient presenting with a clinical picture and history strongly suggestive of myocarditis depends on the severity of myocardial involvement. Many patients will present with a relatively mild disease, with minimal or no respiratory compromise and only mild signs of congestive heart failure. These patients require close monitoring to assess whether the disease will progress to worsening heart failure and the need for intensive medical care. Experimental animal studies[21,133] suggest that bed rest may prevent an increase in intramyocardial viral replication in the acute stage; thus, it appears prudent to place patients under this restriction at the time of diagnosis. Normal arterial blood oxygen levels should be maintained for any patient with compromised hemodynamics resulting in hypoxemia.

Although no specific therapy aimed at reversing myocardial injury is currently widely recommended, maintenance of cardiac

output at levels that supply adequate tissue perfusion and prevent metabolic disturbances is essential. In cases of congestive heart failure, digitalis may be used and has effected dramatic improvement in some instances.[72] During periods of acute inflammation, the myocardium may be overly sensitive to digitalis, and thus rapid administraiton to achieve therapeutic levels should be avoided. Generally, the oral route is preferred and a dose of 0.03 mg/kg rather than 0.04 mg/kg should be used as a total "digitalizing dose." Half of this should be given initially and the remaining half given in two divided doses at 8-hour intervals. Maintenance therapy should be tailored at achieving adequate therapeutic serum levels.

Diuretics are frequently administered in conjunction with digitalis to patients in congestive heart failure. Though there is no direct beneficial effect on the myocardium, removal of excess extracellular fluid volume may help to improve cardiac function. Diuretics should be administered cautiously inasmuch as too rapid a removal of extracellular volume may result in shock. In addition, excessive loss of K^+ ion with the diuresis may exacerbate digitalis toxicity. We recommend furosemide in a dosage of 1 mg/kg/dose. Frequency of administration depends on the patient's clinical state; if three times daily dosing is required (total daily dose >2 mg/kg/day), it may be necessary to add a potassium-sparing diuretic such as spironolactone.

Newborns may present in shock. Blood pressure is usually maintained at or near normal levels until late in the course and thus is not a sensitive indicator of the severity of illness. Rather, close attention to the adequacy of peripheral perfusion, heart rate, and urine output will give the clinician a better picture of the hemodynamic status of the infant. Though the hearts of these infants and children generally respond poorly to volume loading, selected patients may temporarily respond to boluses of 5 mL/kg of 5% albumin in Ringer's lactate or a transfusion of packed red blood cells if a concomitant anemia exists. High central venous filling pressures of 12 to 18 mm Hg may be required to sustain adequate cardiac output, in contrast to 5 mm Hg in a child with a normally functioning heart.

When these measures fail to re-establish an adequate cardiac output, a positive inotropic agent is administered. We generally prefer dopamine in a dose of 2 to 10 μg/kg/min to support blood pressure and effect some degree of dilation of the renal vasculature. As the dose increases toward 20 μg/kg/min, dopamine exerts an increasingly dominant alpha-adrenergic effect and may increase systemic peripheral vasculature resistance; therefore, we usually avoid doses above 15 μg/kg/min. Dobutamine, which is a sympathomimetic amine that stimulates $beta_1$, $beta_2$, and alpha-adrenergic receptors, is frequently used in combination with dopamine. Dobutamine exerts significant positive inotropy while reducing left ventricular filling pressure. Its advantage is that it does not effect as positive a chronotropic response as dopamine and seems to cause less ventricular irritability (i.e., less ventricular ectopy) than does dopamine. When used in combination with dopamine at low doses (<10 μg/kg/min), dobutamine, in doses of 10 μg/kg/min or more, may result in a significant increase in ventricular contractility while avoiding a concomitant sinus tachycardia that may compromise cardiac output. For this same reason, isoproterenol is best avoided in these patients, as the resultant sinus tachycardia that in other patients may improve cardiac output may adversely affect it in this circumstance.

Recently, sodium nitroprusside has been used extensively in children, especially in the early postoperative period. Cardiac output is improved by the ability of this agent to reduce systemic arterial resistance and thus ventricular filling pressure. In patients with myocarditis, sodium nitroprusside may be used in conjunction with the above-mentioned positive inotropic agents if hypotension is not present. In addition, bedside assessment of cardiac output using thermodilution techniques after placement of a Swan-Ganz catheter can greatly aid in the pharmacotherapy of the altered hemodynamic profiles in these patients. When chronic oral therapy is possible and hypotension is not present, an afterload reducing drug such as captopril, an angiotensin-converting enzyme inhibitor, may be used with digitalis and diuretics.

Arrhythmias should be treated vigorously. Supraventricular tachyarrhythmias can often be suppressed with digitalis, which has usually been previously administered for the treatment of congestive heart failure. Ventricular arrhythmias are usually responsive to lidocaine, given in a loading dose of 1 mg/kg followed by a continuous infusion adequate to maintain a therapeutic serum concentraiton (1 to 5 mg/mL). If complete atrioventricular block occurs, a temporary transvenous pacemaker should be inserted. Observation over a 10- to 14-day period (in an intensive care unit) for the return of normal atrioventricular conduction is mandatory. A permanent pacing device should be implanted if complete atrioventricular block persists beyond that time; it can be done as an elective procedure when the patient's condition is stable.

Antibiotic agents should not be given unless a bacterial infection is suspected and appropriate cultures obtained prior to initiating therapy.

The use of immunosuppressive agents in suspected or proven viral myocarditis is controversial. No controlled studies have been done in human beings to prove their efficacy. Some animal studies have suggested an exacerbation of virus-induced cytotoxicity in the presence of immunosuppressive drugs, possibly due to interference with interferon production.[134–136]

Using endomyocardial biopsy to diagnose myocarditis, Mason et al. followed the inflammatory response to immunosuppressive therapy with followup biopsies in a series of 10 patients.[137] Eight of the patients received both prednisone and azathioprine; the remaining two received prednisone alone. Clinical and histologic improvement was seen in four patients. Two patients who had their medications discontinued suffered relapses, which were reversed with reinstitution of therapy. One patient worsened while on therapy and died. Although this was an uncontrolled study, the authors noted that the reversal of congestive heart failure in the two patients who restarted therapy was highly suggestive of the beneficial effect of immunosuppressive therapy.[137] Another study found definite hemodynamic and histologic improvement in seven of nine patients treated with a combination of prednisone and azathioprine. However, after discontinuation of therapy for 4 months, only four of seven patients still showed improvement. One patient improved with reinstitution of therapy, while two patients deteriorated.[138] In another study, endomyocardial biopsies were performed in 12 patients with high-grade ventricular arrhythmias and no other known underlying heart disease.[116] Lymphocytic myocarditis was seen in 50% of this group. These six patients were then treated with prednisone and azathioprine. At followup, five of the six patients had been cured of their arrhythmia; this finding correlated with disappearance of their lymphocytic infil-

trates on repeat biopsy.[116] Again, this was an uncontrolled study, but the results implied a causal relationship between therapy and outcome.

One recent study illustrates the confounding nature of this disease.[117] Nine patients were treated with single or combined immunosuppressive therapy. Improvement was seen in four patients; however, six of 18 patients who did not receive therapy also improved, nullifying any statistically significant difference between the two groups.[117]

Kereiakes and Parmley[139] have tabulated the results from most of the studies to date showing the effects of immunosuppressive therapy. Sixty percent of 82 biopsy-proven cases of myocarditis showed improvement with therapy. Patients who had lower grade changes apparently did better than those with greater involvement. Complications associated with immunosuppressive therapy, including opportunistic infections[9,137] and a cushingoid state,[136] should be taken into account before administration of these drugs. Steroids have also been used in diphtheritic myocarditis[140] but have not been shown to be effective in preventing ECG changes or the associated neuritis. Controlled studies are now underway in the adult population to address the usefulness of immunosuppressive therapy; a similar study should be undertaken in children before firm recommendations concerning the use of immunosuppressive therapy in this disease can be given to clinicians.

The prognosis of acute myocarditis in newborns is poor. A 75% mortality was found in 25 infants with suspected coxsackievirus B myocarditis.[16] The highest mortality occurred in the first week of the illness. The six infants who survived had no apparent sequelae, although long term followup was not reported. Older infants and children have a better prognosis, with a mortality rate between 10 and 25% in clinically recognizable cases. Hastreiter and Miller[60] reported complete recovery in 50% of their patients. Twenty-five percent of the patients continued to have an abnormal ECG or chest radiograph even though they were clinically asymptomatic. Abnormalities in the resting ECG may not be seen, but may be brought out with exercise.[141] Adult patients who recover may be asymptomatic at rest or with light exertion but may demonstrate a reduced working capacity with exercise stress testing.[142]

The cause of the disease may affect prognosis. Patients who develop conduction abnormalities or arrhythmias with diphtheritic myocarditis have a poor progrnosis; some investigators report a 100% mortality rate in patients with conduction disturbances[127] or supraventricular tachycardia.[90]

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CHAPTER 92

Pericarditis

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The pericardium is a bag that surrounds the chambers of the heart, the origins of great arteries, and the junction of the heart with the systemic and pulmonary veins. Although many diseases can affect the pericardium, including trauma, neoplastic diseases, drug-induced diseases, connective-tissue disorders, sensitivity states, autoimmune diseases, metabolic problems, and congenital abnormalities, the infectious diseases are most important in the pediatric population. Therefore, this chapter discusses in detail the causes and pathophysiology of infectious pericarditis. Other chapters in this book deal with pericardial tumors and postpericardiotomy syndrome including the anatomy and function of the pericardium as well as the physiology of pericardial effusion and some aspects of constrictive pericarditis.

Inflammation of the pericardium may result from a variety of nonbacterial microorganisms or may even occur with a number of noninfectious illnesses. In any case, the responses of the pericardium are limited to: 1) acute inflammation, 2) effusion with or without tamponade and, 3) fibrosis with or without constriction.[1] Untreated purulent pericarditis is rapidly fatal. Therefore, it is important to suspect the disease early and approach the diagnosis aggressively. This aspect of pericarditis will be stressed in this chapter.

ANATOMY AND FUNCTION

The pericardium is composed of two loosely approximated layers, the visceral and the parietal pericardium. The visceral pericardium is made up of mesothelial tissue that closely follows the contour of the heart and extends for a short distance beyond the atria and ventricles onto the great vessels. The outer parietal pericardium is a more fibrous structure composed of layers of collagen interlaced with elastic fibers. The pericardial sac is attached to the diaphragm below, the sternum in front, and the thoracic vertebrae, esophagus, and aorta posteriorly. It is surrounded by the lungs on either side and is related closely to the main bronchi and the mediastinal lymph nodes. The phrenic and vagus nerves supply a network of pain fibers to the parietal pericardium.

The dynamics of the pericardial fluid are poorly understood. The pericardial membrane is active in the transfer of water, electrolytes, and relatively small molecules. Fluids of large molecular weight, however, are absorbed poorly from the pericardial space since lymphatic channels are sparse and drainage must occur primarily through the epicardial capillaries.[2]

The function of the pericardium has been summarized by Ainger:[3] 1) prevention of overdistension of the heart, 2) protection of the heart from infection and adhesions, 3) maintenance of the heart within a fixed geometric position within the chest, and 4) regulation of the interaction between the stroke volumes of the two ventricles.

POPULATION AND INCIDENCE

In an extensive literature review of purulent pericarditis, Boyle reported that approximately half of 425 cases occurred in children younger than 13 years of age.[4] Nonetheless, acute purulent pericarditis is diagnosed infrequently. Pericardial disease of all etiologies occurs approximately once per 850 hospital admissions.[5] From 1962 to 1974, 67 cases were recognized at St. Louis Children's Hospital.[5] Twelve of these children (18%) had purulent

pericarditis. There appears to be a predominance of cases in children under 2 years of age. Keith observed that 90% of acute pericarditis in these infants is purulent.[6] A marked male predominance (77%) at all ages is reported by Boyle;[4] however, the review by Gersony and McCracken of 50 infants with purulent pericarditis indicates nearly equal sex distribution (56% males).[7] Feldman et al.[8] showed a 57:43 distribution of males:females.

ETIOLOGY

Primary purulent pericarditis is rare and accounted for only 7 of 50 cases reported by Gersony and McCracken.[9] The disease is associated most often with infection from another site with hematogenous or direct spread to the pericardium. Feldman[8] reviewed all cases of bacterial pericarditis reported in the English language literature from 1950 to 1977. Including his 6 cases, 162 reports were cited. Bacteria were isolated in 146 of 162 cases (90%). No other infection was found in 10 patients. The most common concomitant site involved was the lung, especially for Staphylococcus aureus, Hemophilus influenzae, and Streptococcus pneumonae. When septic arthritis, osteomyelitis, or skin infections were found, S. aureus most often was the cause of pericarditis. Neisseria meningitides and H. influenzae most often were responsible for concomitant meningitis and pericarditis.

Prior to the introduction of antibiotics, the pneumococcal and streptococcal organisms were the most frequent causes of purulent pericarditis in children. The majority of cases were associated with pulmonary infections. Nearly half the patients with streptococcal pericarditis were associated with postinfluenza pneumonia. Hemolytic streptoccoci were isolated most often, whereas 10% were nonhemolytic streptococci and 5% were Staphylococcus viridans.[4] Kauffman et al. reviewed 113 cases of pneumococcal pericarditis reported since 1900.[10] Preceding pneumonia was present in 93% and empyema in 66%. Pericarditis was felt to be a late event resulting from delay in appropriate therapy for pneumonia.

S. aureus is the most common organism responsible for purulent pericarditis in children.[4,7,8,11,12] Prior to the use of antibiotics, it was responsible for only 17% of cases.[4] Most cases result from hematogenous seeding of the pericardium from staphylococcal pneumonia with empyema, acute osteomyelitis, or soft-tissue abscesses. Occasionally, the pericardium is infected during the course of staphylococcal endocarditis. S. aureus is the organism recovered most frequently when purulent pericarditis develops within 3 months of open heart surgery. The clinical course of acute staphylococcal pericarditis is dominated by severe toxemia. In addition to the necrotizing infection produced by S. aureus, the organism often releases a potent exotoxin which produces shock and contributes to the high mortality. S. aureus was isolated from 73% of infants who died of purulent pericarditis in the series reported by Gersony and McCracken.[7] It was responsible for 50% of cases in children between 1 and 4 years of age in the review by Feldman.[8] In seven cases in children younger than 1 month of age, S. aureus was isolated in four. This finding is corroborated in more recent literature from other countries. A review of 53 cases in Nigerian children found S. aureus and Mycobacterium tuberculosis to be equally as common.[13] In New Guinea, 100% of patients less than 18 years of age between 1979 and 1982 had S. aureus isolated as the causative agent.[14] In both reviews, coincident lung infection was found most commonly.

The second most frequently encountered organism is H. influenzae, usually type b. It was responsible for 22% (35 of 163) of the cases in Feldman's review.[8] Of the 18 isolates that were typed, all were type b. A single site of coexisting infection, the lung, was seen in 16 of 35 cases. Meningitis, as a single other site, was found in 5 of 35 and multiple involvement was found in 7 of 35 patients.[5] Cheatham et al.[15] reviewed nine cases of pericarditis in children due to H. influenzae between 1975 and 1979. Seven of the nine patients were younger than 1 year of age and 7 of 9 had either an upper respiratory tract infection or pneumonia diagnosed 6 weeks to 2 days prior to the onset of illness. Two patients had coexisting meningitis. Interestingly, in the reviews from New Guinea and Nigeria, H. influenzae was not found as a cause of pericarditis in children.[13,14]

Dajani et al.[16] reported that in 292 cases of H. influenzae disease, no cases of pericarditis were found, and other authors have reported only 3 cases of pericarditis in 83 consecutive cases of H. influenzae disease. Leggiardo et al.[17] recently reported two cases of H. influenzae pericarditis developing in children while they were receiving intravenous ampicillin for suspected sepsis. Thus, it is apparent that H. influenzae is becoming an increasingly more common agent responsible for pericarditis in the 1980s than in previous decades. Echeverria et al. summarized 33 cases from the literature.[9] Pulmonary infiltrates and empyema were seen in 64% of patients. Nearly 85% had symptoms of an upper respiratory infection in the preceding 5 to 12 days.

Pneumococcal, streptococcal, and meningococcal pericarditis have diminished in frequency since the introduction of penicillin.[4] Pericardial involvement occurs in about 5% of young adults with meningococcemia.[18,19] The clinical course generally is milder than that observed with other types of purulent pericarditis. Pericardial involvement rarely is present at the time of hospital admission. Pericarditis became apparent by the third day in 13 of 17 patients reported by Dixon and Sanford. In some, it did not occur until late in the course of therapy. Whether this late-onset pericardial effusion is a part of the meningococcal infection or is related to penicillin hypersensitivity has been debated in the literature.[18,20–22]

Occasionally, other microorganisms may cause acute purulent pericarditis. Feldman[8] reported that 11 of 146 cases (8%) of pericarditis in children were due to Pseudomonas aeruginosa. It can occur with pneumonic tularemia, salmonellosis, sepsis from enteric bacilli, listeriosis, and disseminated gonococcal disease.[4] Anaerobic bacteria also should be suspected when pericarditis develops in association with lung abscess, intra-abdominal infection, or a penetrating wound. Callanan et al.[23] reported the rapid development of constrictive pericarditis after purulent pericarditis due to anaerobic streptococcal infection. The child had a history of blunt trauma to the chest 3 weeks before developing cardiac tamponade with no evidence of a penetrating wound. The incidence of anerobic infection may be underestimated due to improper handling of specimens for culture.[8]

Mycobacterium tuberculosis, once a common cause of acute pericarditis in the United States,[24] now is responsible more often for chronic pericardial disease. It is a complication of miliary tuberculosis and, rarely, a primary infection. In the series of 2500 children with tuberculosis reported by Lincoln,[25] pericarditis was diagnosed in 0.4% and found at necropsy in 5% of patients. A review of 100 cases of tuberculous pericarditis in South African blacks by Desai et al.[16] revealed a marked male predominance

(72%). The duration of symptoms in the vast majority of patients was from 0 to 120 days and consisted of cough and peripheral edema. Most patients were febrile and in congestive heart failure. Generalized lymphadenopathy was seen in nearly 30% of patients, pulses paradoxus in half and a friction rub was audible in 25%. Of the 52 patients who had pericardiocentesis, 40% yielded fluid but none were positive for acid-fast bacilli. Pericardial effusion was demonstrated in 82 patients, 16 of whom died of tamponade and another 16 of whom went on to develop constricting pericarditis.

Orbtals and Auroli[26] describe the four stages of tuberculous pericarditis as follows: 1) dry, 2) effusive, 3) absorbtive, and 4) constrictive. Granulomas usually are found in the dry stage and heal with no sequelae. The effusive stage is common with tuberculous lymphadenitis and usually 15 to 200 ml of fluid accumulates in the pericardial space. The absorptive stage is characterized by thickening of the pericardium with fibrin deposition. Further fibrin deposition plus calcification occurs during the constrictive phase. The disease may progress through all stages or remain in one stage alone.

Latent infection in the mediastinal lymph nodes with spread directly into the pericardium is thought to be the mode of involvement with M. tuberculosis.[26] The lymph nodes at the tracheal bifurcation are often the source.

Histoplasma pericarditis generally occurs with pulmonary rather than disseminated disease.[27] Coccidioidomycosis[28] and, rarely, blastomycosis[29] also may cause pericardial disease. Other pathogenic fungi include Aspergillus and Candida. These are more serious considerations in patients who are immunosuppressed or are on long-term broad-spectrum antibiotics or following cardiac surgery.

PATHOLOGY AND PATHOGENESIS

Pericarditis begins with fine deposits of fibrin adjacent to the great vessels; this causes the pericardial membrane to lose its smoothness and translucency. Numerous granulocytes may extend into the myocardium.[30]

Bacterial pericarditis most commonly results from direct extension of infection from involved lung and pleura. Pulmonary infections may spread to the pericardium through the bronchial circulation.[31] Pericarditis frequently arises, however, from infection elsewhere that is transmitted hematogenously. It also may result from immunologically induced antibody response to a primary infection.

As pericardial fluid accumulates, intrapericardial pressure rises. The rate of rise is a function of both the speed of accumulation and the compliance of the pericardium. With slow accumulation of fluid, large volumes can be accommodated because of the gradual expansion of the parietal pericardium. As the compliance of the pericardium reaches its maximum, however, further accumulation of even small volumes of fluid results in an abrupt increase in intrapericardial pressure. If pericardial fluid accumulates rapidly, marked elevation in intrapericardial pressure may occur with much smaller volumes of fluid. As little as 100 ml can cause severe tamponade in a small child, whereas up to 3 L may accumulate slowly in an older child and not result in tamponade.[3]

The most significant hemodynamic effect of pericardial effusion is restriction of ventricular filling. Ventricular end-diastolic, atrial, and venous pressures rise on the right and left heart equally. When restriction to ventricular filling becomes more pronounced, there is a fall in ventricular stroke volume and cardiac output. In an attempt to maintain cardiac output, tachycardia and peripheral vasoconstriction are seen. In addition, systemic arterial blood pressure and pulse pressure are reduced markedly.

Tamponade occurs when these compensatory mechanisms fail to maintain adequate cardiac output.

CLINICAL MANIFESTATIONS

A diagnosis of purulent pericarditis should be suspected in any patient with septicemia who develops cardiomegaly. The classic signs and symptoms of pericarditis are as follows: 1) precordial pain, 2) pericardial friction rub, 3) evidence of cardiac fluid, and 4) muffled heart sounds.[32] Chest pain is not a frequent symptom, especially in young children; the reported percentages vary from 15 to 80.[2,4,6,7,12,33–35]

The most common symptoms and signs of pericarditis are fever, tachypnea, and tachycardia. These also are presenting features of associated systemic infection. However, if there is enlargement of the cardiac shadow radiographically, with or without a friction rub, and the tachypnea and tachycardia are out of proportion to the fever, either myocardial dysfunction or pericarditis should be suspected. An evanescent or ubiquitous rub may be present. The typical sound of a rub is that of a high-frequency murmur[36] that may be to and fro or triphasic but may not have any correlation with the cardiac cycle.[37] The rub frequently is heard better with the patient leaning forward or kneeling.[37] A rub may be differentiated from a murmur by pressing the diaphragm of the stethoscope firmly against the chest wall; this amplifies the rub, and the typical scratchy quality becomes more apparent as one opposes the visceral and parietal pericardium by compression of the chest. Rubs have been known to increase with inspiration.[38] Although it is generally true that a rub is less likely to be heard when there is a large effusion, it still may be present.[37] The heart sounds usually are muffled, and the palpable ventricular impulse generally is diminished. Both of these findings, however, may be found in congestive heart failure; they may be absent with tamponade.

Signs of cardiac tamponade may be an early complication of pericarditis in association with a systemic infection. Cardiac tamponade means that there is compression of the heart by a tense pericardial sac, usually full of fluid, resulting in a decrease in venous return to the cardiac chambers and a decrease in cardiac output. During inspiration, intrathoracic pressure falls, and there is an increase in venous return to the cavae. The tense pericardial sac limits the amount of blood that can enter the right atrium because of diastolic compression; therefore, there is a paradoxic rise in jugular venous pressure during inspiration (Kussmaul sign)[39] (Fig. 92–1).

During inspiration, there is normally a small drop in systolic blood pressure and cardiac output due to an increase in pulmonary venous capacitance. This is exaggerated with pericardial tamponade (greater than 10 mm Hg drop in blood pressure) because of the restricted inflow into the cardiac chambers. This clinical sign has been called paradoxic pulse, but it is actually an exaggeration of the normal respiratory cycle[40] (Figs. 92–2A and 92–2B).

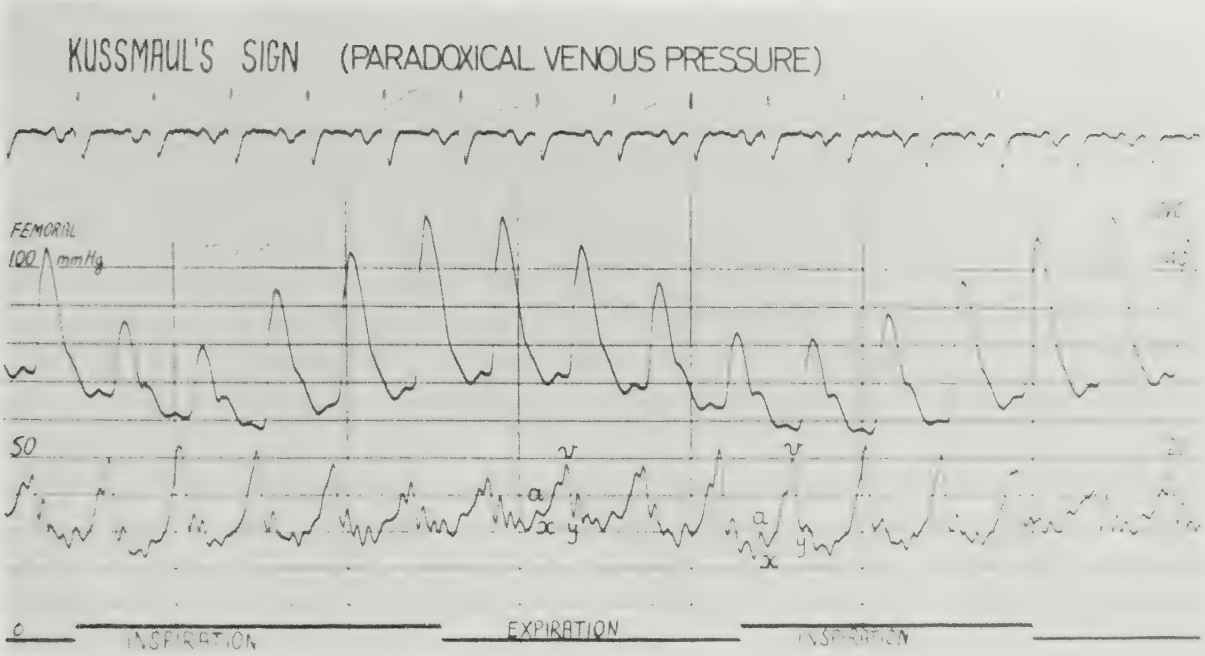

Fig. 92–1. Simultaneous recording of right atrial and femoral artery pressures. Note the increased V wave and exaggerated decrease in femoral artery pulse with inspiration.

DIAGNOSIS

Radiographic appearance of a rapidly increasing cardiothoracic ratio without increasing pulmonary vascular markings is more suggestive of pericardial effusion than congestive heart failure secondary to myocardial dysfunction (Fig. 92–3). Fluoroscopy alone is generally of little value; both myocardial dysfunction and pericarditis can impair cardiac contractility.

The size of the pericardial shadow does not necessarily indicate the severity of hemodynamic effects. This is a function of the rapidity of accumulation and the volume of pericardial fluid. Thus, when acute infection results in sudden cardiac tamponade, heart size may be normal. A large globular heart shadow with no evidence of increased pulmonary vasculature—particularly in a patient who has signs of right heart failure—strongly suggests pericardial disease. The lack of pulmonary overcirculation will help to distinguish this from myocarditis; however, this may be difficult to determine if there also are pulmonic infiltrates.

Lane and Carsky demonstrated the potential of a plain lateral chest film to demonstrate pericardial effusion.[41] The anterior mediastinal and subepicardial "fat stripes" were separated by more than 2 ml in 27 of 42 cases of proven effusion. However, 5 of 15 "negative" films and none of the "positive" films were seen in patients with purulent pericarditis. Obliteration of the retrosternal space without evidence of thymic or right ventricular enlargement also suggests pericarditis.

LABORATORY EVALUATION

Electrocardiogram

The extent of electrocardiographic abnormalities may be explained by the amount of pericardial effusion and the presence of superficial myocardial injury or myocarditis. Pericardial effusion gives rise to low-voltage QRS complexes. This is the result of the damping effect of pericardial fluid between the chest wall and the myocardium. Accumulation of fluid and fibrin under pressure also may produce an injury pattern manifest by ST segment deviation. Over 90% of patients have elevation of the ST segment, which occurs most frequently in leads I, II, V_5, and V_6. Widespread T-wave inversion indicative of epicarditis may be seen in the same leads in which ST segment elevation occurs.

Spodick has described four stages of electrocardiographic changes in acute pericarditis.[42] In stage I, pronounced ST segment elevation is present, and depression of the PR segment may be noted. In stage II, the ST segment begins to return toward the isoelectric line, the amplitude of the T wave diminishes, and the PR segment is depressed. By stage III, the ST segment has returned to the isoelectric line and the T-wave inversion occurs. An incompletely inverted T wave (a diphasic wave or an upright T wave with a notched summit) sometimes is observed. In stage IV, these changes may resolve completely. T-wave abnormalities, however, may persist for life and do not necessarily indicate active disease.

Ginzton and Laks[43] compared the electrocardiograms of 19 patients with acute pericarditis with 20 healthy patients. By forming a ratio of the amplitude of the ST segment and T-wave height in all patients, a value of 0.25 or greater in lead V_6 had a positive and negative predictive value of 1.0 for determining the presence of pericarditis. This also was true in leads I, V_4, and V_5 though the predictive values were not as high as in lead V_6. Using Spodick's criteria in their patients, Ginzton and Laks were unable to distinguish healthy normals from acute pericarditis patients. Their method may therefore prove to be more reliable, though a large study in children has not been performed.

Electrical alternans is seen in the presence of a large pericardial

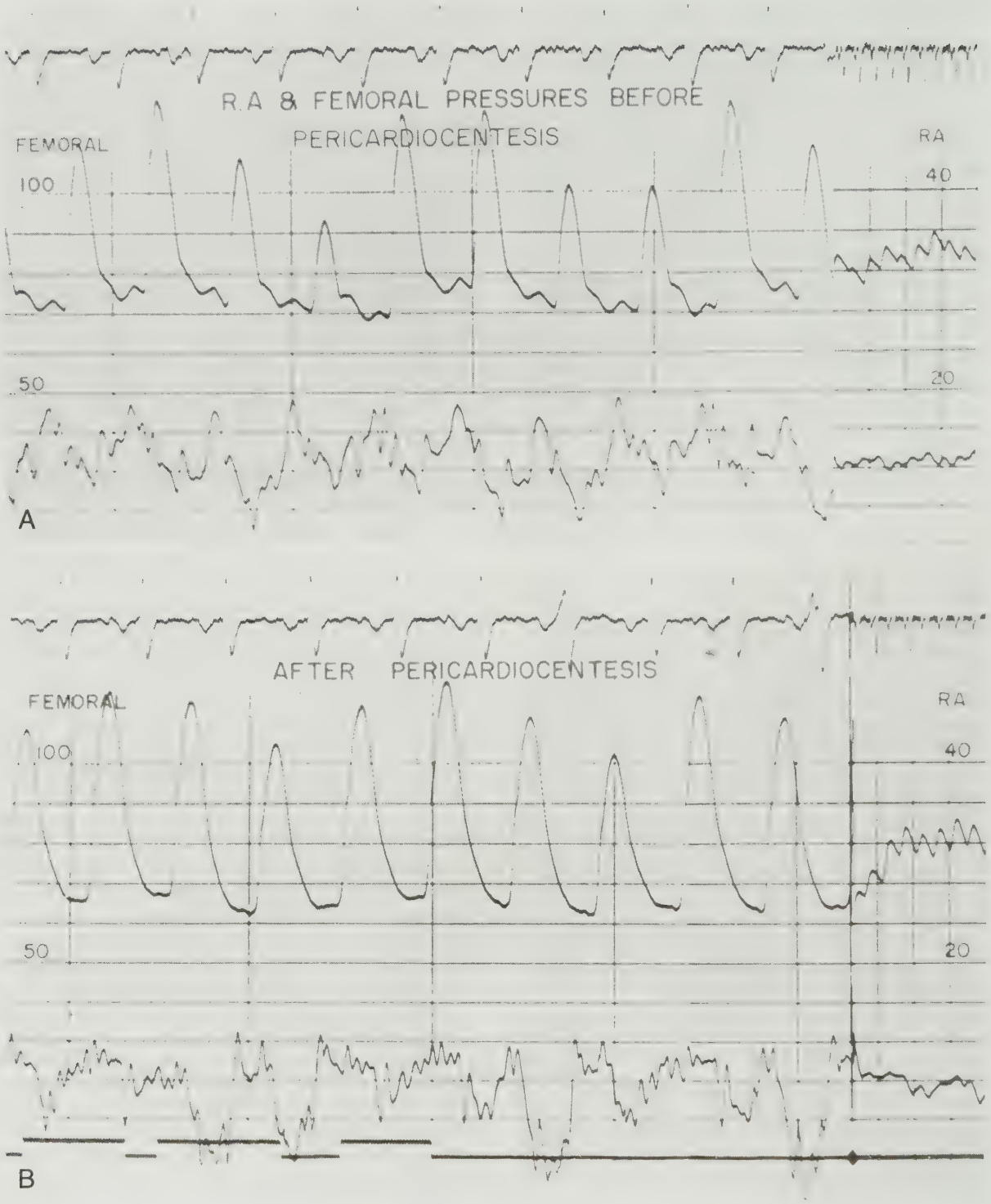

Fig. 92–2. Recordings of femoral artery and right atrial pressures (A) prior to and (B) following pericardiocentesis. In (A), there is an exaggerated decrease in fall of femoral artery pressure with inspiration as well as a sustained increase in right atrial pressure. (B) demonstrates a more normal variation of femoral pressure and a lower right atrial pressure.

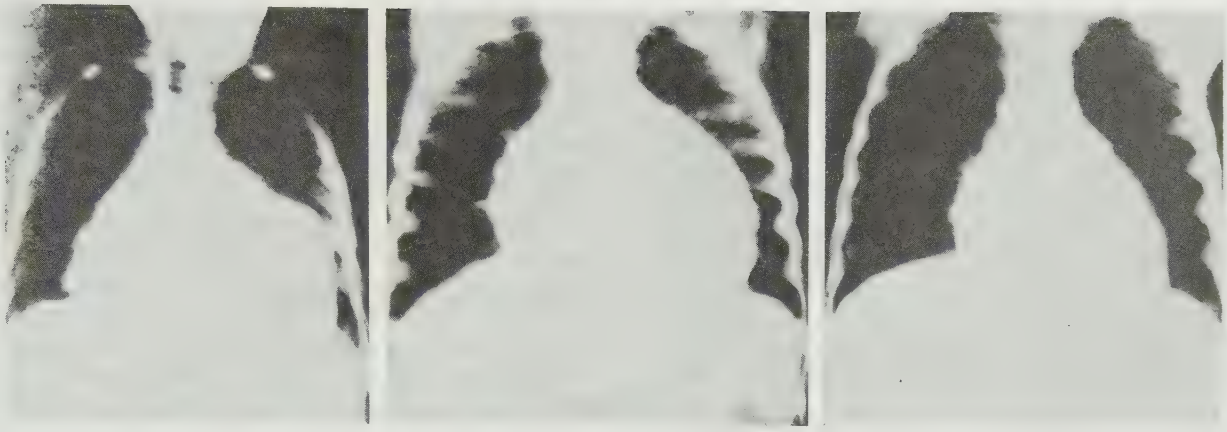

Fig. 92–3. A patient with pericarditis. The first two radiographs demonstrate an enlarged cardiac shadow without an increase in pulmonary vascular markings. The last shows a marked decrease in apparent heart size after pericardiocentesis.

effusion. This refers to the alternation in electric amplitude of the T wave and the QRS complex with each cardiac cycle. Electrical alternans is thought to result from the rotational and pendular motion of the heart suspended in pericardial fluid.

Deviations from classic patterns occasionally occur, but it is not uncommon to have single electrocardiographic changes. For example, all 12 children reported by Okoroma et al. had ST segment elevation, while only 3 had concomitant low voltage.[30]

Spodick[44] has pointed out that although many textbooks cite the frequent occurrence of dysrhythmias with pericarditis, they are an unusual occurrence in the absence of coexisting heart disease. Twenty of 49 patients with acute pericarditis had no underlying heart disease. Seven had no dysrhythmias documented on 24-hour Holter monitoring and 10 of 20 had infrequent single ectopic beats. Only three patients had supraventricular tachycardia.

Echocardiogram

M-mode echocardiography is the most sensitive method for diagnosis of significant pericardial effusion.[45,46] With a small to moderate effusion, only a "fluid space" is noted posteriorly. However, with a greater effusion, fluid is seen anteriorly and posteriorly, and the septal motion becomes grossly abnormal. The heart may give the appearance of freely swinging (Fig. 92–4). Newer echocardiographic techniques, such as two-dimensional sector scanning, are no more useful than the conventional M-mode.

Laird et al.[47] found pericardial effusions on M-mode echocardiograms in 20% of patients with H. influenzae meningitis. The counter immunoelectrophoresis was usually positive for antigen of H. influenzae, and the amount was usually 20 ml or less. However, the majority of cases were asymptomatic and resolved spontaneously with resolution of the meningitis. Thus, the clinical significance of this pericarditis may be minimal. Laird et al. felt that this technique was of limited value in patients without evidence of cardiac involvement.

Radionuclide Imaging

Occult or unsuspected pericarditis also has been discerned with the use of radionuclide techniques. Greenberg et al.,[48] using iridium-111, and Shreiner et al.,[49] using gallium-67, demonstrated the presence of purulent pericarditis in an immunocompromised host and posttraumatic patients, respectively.

Cardiac Catheterization

A pericardial effusion also may be diagnosed by noting a discrepancy between the position of a catheter placed adjacent to the lateral wall of the right atrium and the right cardiac border. An injection of radiopaque contrast material into the right atrium may further delineate these findings. Pressure measurements at the time of cardiac catheterization reveal the elevated right atrial pressure and further emphasize the exaggeration of venous, systemic, and left ventricular pressures imposed by inspiration. Injection of CO_2 or air into the pericardium percutaneously may delineate further the pericardial effusion fluoroscopically and differentiate freely moving fluid from loculated areas (Fig. 92–5). Radionuclide imaging also has been helpful in establishing a diagnosis of pericardial effusion.[50,51]

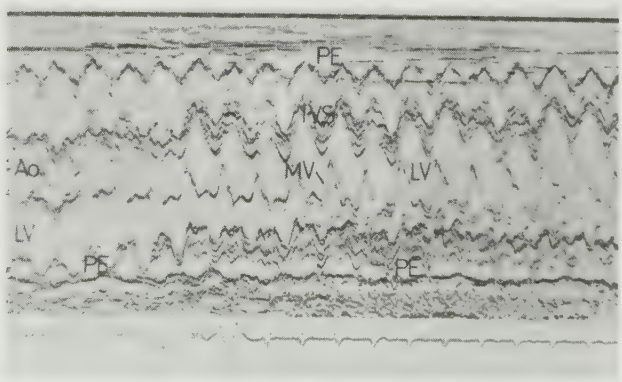

Fig. 92–4. Serial M-mode tracing of a child with pericarditis and pericardial effusion. There is an effusion both anteriorly and posteriorly. Ao—aorta; IVS—Interventricular septum; LV—left ventricle; MV—mitral valve; PE—pericardial effusion.

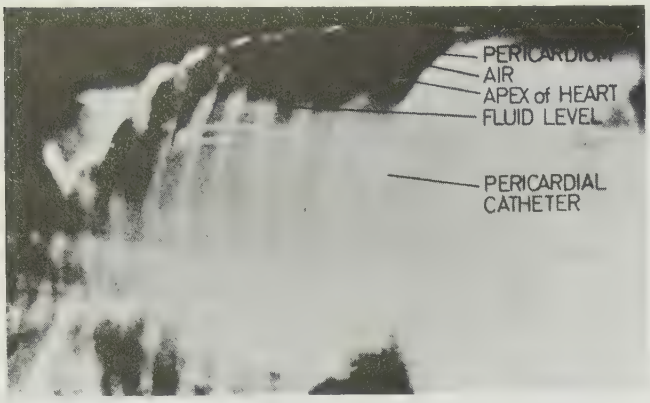

Fig. 92–5. Chest radiograph of a patient lying on right side with a catheter in the pericardium. Air has been injected through the catheter, outlining the pericardium and fluid within the sac.

Pericardiocentesis

The diagnosis of purulent pericarditis is established definitively only by direct examination of pericardial fluid. Purulent fluid is characterized by a predominance of polymorphonuclear leukocytes; however, this also may occur early in the course of viral and tuberculous pericarditis. Proper handling of pericardial fluid is crucial to recovery and identification of the etiologic agent: first, place fluid directly into broth capable of supporting aerobic and anaerobic microorganisms. Fluid also should be plated directly onto agar media such as blood agar, chocolate agar, and MacConkey agar. In addition, cultures should be submitted for M. tuberculosis, fungi, and viruses. Next, several slides should be prepared for immediate examination by Gram stain and stain for acid-fast bacilli. Unstained slides should be stored in case of controversy or the need for special histochemical stains. A sample of pericardial fluid may be submitted for detection of bacterial antigens by latex agglutination or countercurrent immunoelectrophoresis or for detection of staphylococcal techoic acid antibodies. These techniques are useful, particularly if the patient has received prior antimicrobial therapy. The yield from these procedures may be increased by concomitant examination of the serum and urine of the patient.

The causative microorganism is isolated from blood cultures in the majority of patients. When indicated, cerebrospinal fluid also should be cultured. Since purulent pericarditis often follows infections of the lung or pleural space, thoracentesis or direct lung aspirate will reveal the etiologic agent in many cases. Documentation of empyema together with evidence of pericardial disease correlates highly with purulent pericarditis. Van Reken and associates, however, have reported an interesting case of H. influenzae type b pneumonia and empyema in a patient from whom only Coxsackie A-9 virus was isolated from nonpurulent pericardial fluid.[52]

Acid-fast bacilli are present on stained smears of pericardial fluid in 15 to 42% of patients with tuberculous pericarditis.[24] Examination of pericardial biopsy will increase the frequency of identification of M. tuberculosis. Not all patients will react to intermediate-strength PPD (67%) and second-strength skin tests might be necessary. The anergic state seen with miliary disease must be excluded.

Grossly bloody pericardial fluid is noted frequently in patients with Histoplasma pericarditis, and an aspirate of the effusion reveals a predominance of mononuclear leukocytes. Growth of H. capsulatum from pericardial fluid rarely is successful. Elevation of the yeast phase of the complement-fixation titer in pericardial fluid allows a more rapid diagnosis.[27] Serum precipitin antibodies to H. capsulatum also indicate acute histoplasmosis.

DIFFERENTIAL DIAGNOSIS

Any patient with a rapidly increasing heart size in the absence of increasing pulmonary vascular markings should be suspected of having a pericardial effusion. Purulent pericarditis must be differentiated from pericardial effusion due to collagen diseases, other infectious agents (viral, tuberculous, rickettsial, protozoan), neoplastic disorders, metabolic disorders, and congestive heart failure.[8] In addition, glycogen storage disease, congenital heart disease, primary myocardial disease, cardiac tumors, and coronary artery aberrations (anomalous origin from the pulmonary artery, medial wall necrosis, and mucocutaneous lymph node syndrome) may be confused with pericardial effusion.[8] Appropriate analysis of pericardial fluid, as described, generally permits differentiation of purulent pericarditis from pericarditis caused by other disorders.

TREATMENT

Purulent pericarditis is a potentially life-threatening illness that requires the following: 1) pericardial decompression and open drainage, 2) appropriate antimicrobial therapy, and 3) intense supportive therapy.

Ainger has stated that over half the children with purulent pericarditis require early or emergency drainage of the pericardium for relief of critical tamponade.[3] Although bedside needle pericardiocentesis may be life-saving or necessary for rapid diagnosis, Flower and Manitsas have reported three deaths related to pericardiocentesis performed by inexperienced physicians.[37] Complications include arrhythmias resulting from myocardial injury, laceration of the coronary arteries leading to hemopericardium and tamponade, and pneumothorax. Ledbetter[53] has described a 10-year-old girl with staphylococcal pericarditis who developed an aortic aneurysm after multiple pericardiocentesis for recurrent tamponade. The subxiphoid approach is recommended, and Hoffman and Stanger[54] describe the proper technique.

Decompression and drainage of the pericardium is safest in a controlled environment such as in an operating room or under fluoroscopy in the catheterization laboratory. If the patient is awake and agitated, premedication with IV diazepam (1 mg/year of age) or ketamine (0.5 to 1 mg/kg) may be given.

If pericardiocentesis is not successful in relieving symptoms and evidence of tamponade continues, immediate surgical drainage is necessary. Multiple attempts may prove unsuccessful and can lead to serious complications. The pus surrounding the heart may be too thick to be aspirated, as has been seen especially with H. influenzae infection.[55] A surgically created pericardial window with a drain sometimes is necessary to remove completely fluid that accumulates rapidly. While preparing to evacuate the peri-

cardial fluid during tamponade, adequate cardiac output can be maintained by stimulating the heart with pharmacologic agents that cause both a chronotropic and an inotropic effect. Isoproterenol administered intravenously at a rate of 0.05 to 0.10 μg/kg/min is our drug of choice. This does not replace evacuating the fluid but gains time until the aspiration or drainage can be performed. Medications that tend to decrease heart rate and intravascular volume are contraindicated as they further compromise the patient. Wyler[56] warns against the use of halothane anesthesia because of the known depressant effect on myocardial function. He described two patients who had reversible cardiac arrest when this agent was used during surgery to relieve tamponade.

Controversy exists regarding the approach and extent of surgery.[37,57–61] Either a left anterolateral thoracotomy through the fifth intercostal space or a subxiphoid approach with removal of the xiphoid process appears best. Most surgeons favor the creation of a pericardial "window"; however, some favor more extensive removal of pericardial tissue. This decision may be influenced by the severity of pericardial inflammation or the presence of bloody pericardial fluid since these have greater potential for producing acute or chronic constriction. Care must be taken during the procedure not to injure the phrenic nerves. Morgan et al.[55] reviewed 15 children with purulent pericarditis between 1971 and 1981. H. influenzae occurred in 7 of 15 patients. Most patients had pericardiocentesis followed by an anterior interphrenic pericardiectomy and recovered completely. In a series of nine children with H. influenzae pericarditis, all received a limited left thoracotomy with subxiphoid approach for pericardiostomy, and there were no deaths.[15]

It must be emphasized that antimicrobial therapy alone is insufficient for the successful treatment of purulent pericarditis. The survival of patients with purulent pericarditis is improved significantly when early pericardial drainage is performed. In the preantibiotic era, draining the pericardium improved the mortality from nearly 100 to 45%.[4] Occasional patients with meningococcal pericarditis have been managed successfully without pericardial drainage.[20] Fyfe et al.[62] described 73 of 79 patients with H. influenzae pericarditis seen between 1928 and 1984. The mortality before 1960 was 64% (7 of 11 patients), though the majority (5 of 7) were reported prior to the antibiotic era. From 1960 to 1969, the mortality was 36%, and from 1970 to 1979 it droppped to 11.5%. Since 1980, there have been 25 reported cases with 0% mortality. Fyfe et al. note that when surgical drainage techniques were used with antibiotic therapy there was no difference in mortality between patients receiving ampicillin and chloramphenicol versus ampicillin alone. This reflects the absence of ampicillin resistant organisms found in these patients.

When the etiologic agent cannot be detected rapidly, the initial antibiotic regimen should consist of two or more drugs. Since S. aureus is a major pathogen, a penicillinase-resistant penicillin such as methicillin, nafcillin, or oxacillin must be included in a dose of 200 mg/kg/24 hr (maximum, 8 g). For the patient who is allergic to penicillin, vancomycin, clindamycin, or a cephalosporin is substituted; some patients who are allergic to penicillin will be sensitive to cephalosporin. In addition, ampicillin should be administered (300 mg/kg/24 hr) to provide protection against streptococci, pneumococci, meningococci, and H. influenzae. Chloramphenicol should be used when disease due to H. influenzae is suspected, until the sensitivity of this organism to ampicillin can be confirmed. An aminoglycoside antibiotic should be added to this combined drug therapy when purulent pericarditis occurs following cardiac surgery, in association with genitourinary infections or in the immunocompromised host. Duration of therapy is empiric and in part determined by the nature of concomitant infection. Generally, once a pathogenic microorganism has been isolated, the most specific antimicrobial agent is continued intravenously for 3 to 4 weeks.

The chemotherapy of tuberculous pericarditis has had a major impact on mortality. Prior to its use, there was an 80 to 90% mortality in the acute phase and the other 10 to 20% dying from constrictive pericarditis or miliary tuberculosis.[26] Presently, the use of three or four drugs including isoniazid, pyrazinamide, rifampin and possibly streptomycin for a period of 9 to 18 months is recommended. Corticosteroids seem to be helpful in reducing the inflammatory response to infection and enhancing the resorption of pericardial fluid.[26] Prednisone, 80 mg, or equivalent doses of other preparations over 6 to 8 weeks also is recommended. In selected cases, pericardiectomy may be indicated to prevent constrictive pericarditis.

Amphotericin B alone or with other systemic agents is indicated for treatment of fungal pericarditis; however, it rarely is required for successful therapy of Histoplasma pericarditis.

General supportive therapy in the acute stage of infection may include the administration of oxygen, volume expansion to increase ventricular filling pressure, and isoproterenol to facilitate systolic emptying. Digitalis and diuretics should be used cautiously and only when indicated by decreased myocardial function. Serial electrocardiograms may indicate the presence of occult arrhythmias and alert the physician to the degree of myocardial involvement. The patient must be monitored carefully for signs of reaccumulation of pericardial fluid and for the development of acute constrictive pericarditis. Strauss et al. reported this complication in 2 of 12 children with purulent pericarditis.[5] Acute constriction may develop within weeks of the initial pericardial infection[33,63] and has been reported as early as the eighth day.[64] Constrictive pericarditis may be suspected by increasing jugular and central venous pressure, weight gain, enlarging liver, worsening dyspnea, and decreased urinary output. The presence of persistent heart failure when the cardiac silhouette is shrinking also suggests the development of constrictive pericarditis. Complete pericardiectomy should be performed promptly when constriction is suspected.

PROGNOSIS

The current mortality of acute purulent pericarditis ranges from 25 to 75%. Accurate statistics, however, are difficult to compute from the literature since the nature and severity of underlying disease have not been considered. Factors that contribute to mortality are 1) delay in recognition; 2) absence of early surgical drainage; 3) presence of cardiac tamponade; 4) degree of myocardial involvement; 5) the etiologic agent (particularly S. aureus); and 6) age of patient. Long-term followup of children with purulent pericarditis is recommended. They should be followed carefully for the presence of a constrictive component as a sequela to the acute infection. Most children, however, recover fully with a return to normal activity.

VIRAL PERICARDITIS

In 1951, Christian suggested that viral infections were responsible for cases of idiopathic or benign pericarditis.[20] A viral etiology, however, cannot be substantiated in many patients.

Etiology

The principal viruses implicated in pericarditis are the Coxsackie group.[65] Adenoviruses have been recovered less frequently.[66] Previous associations with chickenpox, smallpox vaccinations, influenza,[67] influenza vaccinations,[68] and even infectious mononucleosis[69,70] have been reported.

Clinical Manifestations

Generally, there is a history of upper respiratory infections 10 days to 2 weeks preceding onset of symptoms in about 40 to 75% of cases. Fever and chest and abdominal pain are the most common symptoms.[11,20] A friction rub may be heard in 50 to 80% of cases.[35] Children with viral pericarditis generally are less toxic and experience smaller elevations in body temperature than those with purulent pericarditis. Some, however, appear acutely ill. Large amounts of pericardial fluid accumulation and tamponade are rare.

Investigative Techniques

The electrocardiographic, radiographic, echocardiographic, and nuclear-scanning findings described in patients with purulent pericarditis also are observed in patients with viral pericarditis. The peripheral leukocyte count, however, may reveal fewer polymorphonuclear leukocytes than in patients with bacterial pericarditis. Mononuclear cell infiltrates in the pericardium with extension into the myocardium may be seen.

If obtained, pericardial fluid should be sent for cell count and viral culture. Nasopharyngeal and rectal culture also should be obtained and cultured for viruses. Acute and convalescent serum should be obtained so that appropriate titers can be measured if a virus is isolated.

Course and Prognosis

Viral pericarditis generally resolves spontaneously over a 3- to 4-week period.[65] Large pericardial effusions and tamponade are rare.[32] Generally, bed rest for about 1 week and analgesics for pain are the only required therapy. Corticosteroid therapy rarely is necessary. Constrictive pericarditis is rare. Recurrent pericarditis may develop.[65]

CONSTRICTIVE PERICARDITIS

Constrictive pericarditis involves a thick, frequently fibrotic, and sometimes calcified pericardium.[71,72] This generally leads to restriction in diastolic function of the heart.[71] It is most often a late sequela of purulent pericarditis, and its occurrence in pediatrics is controversial. In a review by Boyle et al.,[4] it was estimated that only 3 to 6% of patients with constrictive pericarditis had a previous documented septic illness in pericarditis. Other investigators have indicated that H. influenzae have led to constrictive pericarditis.[5,63,64] Most likely, the constrictive aspect of pericarditis will occur at least several weeks to months following the acute episode.

Historically, constrictive pericarditis occurs most frequently following tuberculous pericarditis and other forms of purulent pericarditis. It has been documented in from 12 up to 35% of patients with known tuberculous pericarditis.[42] For at least one-half of all patients with constrictive pericarditis, no etiology is found.[42]

The constriction usually is a uniform process and affects all cardiac chambers. It has been reported that there may be localized bands that constrict particular aspects of the heart more completely such as in the atrioventricular groove and aortic and pulmonary valve rings. This may create situations that simulate obstructive valvular disease or obstruction to blood flow returning to the heart such as superior vena cava syndrome or cirrhosis of the liver.[73,74]

The thickening and resulting constricting action of the pericardium lead to decreased diastolic volume and compliance of the ventricles with resulting decreased stroke volume and cardiac output. Intracardiac diastolic pressures will be elevated. Because the pericardium is noncompliant, ventricular filling occurs early but reaches its capacity earlier than normal in the cardiac cycle. Therefore, the diastolic pressure stays the same in mid and late diastole, thus producing the characteristic square root signs in the ventricular pressure curve characteristic of constrictive pericarditis.[71] This constrictive effect to the heart creates equal diastolic pressures in all chambers of the heart as well as the pulmonary circulation. Additionally, the expected fall in systemic venous and right atrial pressures or the increase in venous return to the heart during inspiration does not occur. Although pulsus paradoxus is characteristic of cardiac tamponade, it is not as frequently seen in constrictive disease. The heart tries to compensate for its decrease in stroke volume and potential cardiac output by increasing the rate.[75] However, in severe constriction cardiac output is eventually reduced significantly.[76,77]

Frequently, it is difficult to establish the diagnosis of constrictive pericarditis and differentiate it from restrictive cardiomyopathy. One important differentiating finding in constrictive pericarditis is that the right ventricular and pulmonary artery systolic pressures frequently do not exceed 50 mm Hg.[78] Additionally, in restrictive cardiomyopathy, the left ventricular diastolic pressure generally is at least 5 mm Hg greater than the right ventricular pressure as opposed to constrictive pericarditis, in which the diastolic pressures are similar throughout the heart.[79] Also, the ejection fraction generally is normal in constrictive pericarditis.[80] Sometimes, an endomyocardial biopsy may indicate an infiltrative process, thereby confirming the diagnosis of restrictive cardiomyopathy. However, a normal biopsy cannot necessarily exclude that diagnosis.[79]

Obviously, constrictive pericarditis must be corrected by removal of the pericardium. This should be done prior to the occurrence of long-standing myocardial effects.[81]

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CHAPTER 93

Postoperative Inflammatory Syndromes

Sandra K Clapp

There have been great advances in pediatric cardiovascular surgery over the last 30 years. Children with previously fatal cardiac defects can now undergo corrective or palliative operations that enhance both the length and quality of life. With advances in cardiovascular surgery, however, new illnesses have developed that may complicate postoperative recovery. These include postpericardiotomy syndrome and postperfusion syndrome. Common aspects of these illnesses are postoperative fever and malaise, which are generally self-limited. Although rarely fatal, both syndromes prolong postoperative recovery and must be differentiated from other potentially serious operative complications such as endocarditis, wound abscess, pneumonia, atelectasis, and congestive heart failure. The correct diagnosis can be made by recognizing the individual features of each syndrome and by performing appropriate studies to exclude other possible postoperative complications.

POSTPERICARDIOTOMY SYNDROME

Postpericardiotomy syndrome (PPS), the most common of the postoperative inflammatory syndromes, remains a nebulous illness that affects both children and adults in whom the pericardium has been opened. PPS consists of fever beyond the first postoperative week, a variety of symptoms including malaise, pleuropericardial pain, joint pains, decreased appetite, and signs of pleural and/or pericardial inflammation. First observed in the early 1950s in patients operated upon for rheumatic mitral stenosis, PPS was thought to be a reactivation of the rheumatic process.[1,2] Similar findings were described subsequently in nonrheumatic patients undergoing open-heart surgery.[3] Identical illnesses have been reported in patients following myocardial infarction (Dressler's syndrome),[4] and following both penetrating[5,6] and blunt trauma[7] to the pericardium. These illnesses have in common irritation or disruption of the pericardium and underlying myocardium. A common pathogenesis is suspected for Dressler's syndrome, traumatic disruption of the pericardium, and PPS.[5–8]

Incidence

Engle has made major contributions to the understanding of postpericardiotomy syndrome.[3,8–10] A recent report of 400 postoperative children prospectively evaluated for PPS found an overall incidence of 27%.[9] This conclusion agrees with other pediatric and adult series in which the incidence is approximately 30% (range 10 to 60%).[11–17] PPS also has been noted to occur following placement of epicardial leads for pacemaker implantation, although the incidence of this occurence is not known.[18,19] For reasons that are unclear, PPS rarely develops below the age of 2 years, with an incidence in this age group of only 3.5%.[9] Although it may develop following any surgery involving opening of the pericardium, PPS is more common with correction of certain congenital heart defects such as tetralogy of Fallot and ventricular septal defect with pulmonary stenosis.[9] This may be related to the extensive myocardial trauma involved with these operations.[9] Some studies also have noted an increased frequency of PPS in patients who have had prior operations involving the pericardium.[11,16]

Etiology and Pathogenesis

Although there has been much speculation and extensive investigation since the illness was first described, the etiology and

pathogenesis of PPS remain unclear. The original theory that PPS was a reactivation of the rheumatic process[1,2] was disproved when PPS was observed in nonrheumatic patients,[3] and when no supportive evidence of recurrent rheumatic fever could be found.[20–24] Subsequent studies also disproved other secondary infections within or involving the pericardium.[25]

Several authors have noted a seasonal variation in the incidence of PPS and have suggested a new or reactivated viral infection could be involved in its pathogenesis.[8–10,13,15,16] In Engle's group of 400 patients, 70% of those with clinical PPS and antiheart antibodies had a fourfold or greater rise in titer postoperatively to one or more of eight viral agents tested.[9]

Further investigation has suggested that the pathogenesis of PPS might involve an immunologic (autoimmune) component.[8–10,13–15,17,26,27] Many investigators have demonstrated heart-reactive antibodies in the sera of patients who have developed PPS.[8–10,13–15,26,27] The presence of these autoantibodies in high titers correlates well with clinical evidence of PPS.[8–10,13,26,27] Maish, et al.[26] have further investigated the types of autoantibodies and found that 95% of their patients with complete PPS showed antibodies against myocardium and skeletal muscle that included both antisarcolemmal antibodies and antifibrillary antibodies. They noted that antifibrillary antibodies reached a peak 2 weeks after surgery and were primarily IgM, in contrast to antisarcolemmal antibodies, which were predominantly IgG and were seen during the third postoperative week. From the type and timing of appearance of these antibodies in the sera, they suggested that the antifibrillary antibodies are related to a primary immune response after operation whereas the antisarcolemmal antibodies are related to a secondary response.[26]

Opinions differ as to whether the triggering mechanism or "foreign protein" is the surgically damaged myocardium, pericardium, or blood in the pericardial space or a new or reactivated viral inflammation of that same tissue. The end result is proposed to be a delayed hypersensitivity reaction to the foreign stimulating autoantibody production with subsequent development of symptoms.[8–10,13–15,26–29] Other researchers question whether antiheart antibodies cause the syndrome or occur as a consequence of a more diffuse inflammatory process involving circulating immune complexes.[17,27,29–30] It can be summarized from this discussion that further investigation is necessary to determine the exact pathogenesis of this complicated illness.

Diagnosis

Postpericardiotomy syndrome is a febrile illness that occurs 1 to several weeks following an operation in which the pericardium is opened. Although it is usually a single illness, recurrences may occur months or years later.[11,31,32] The fever may be a continuation of early postoperative fever that persists beyond the first postoperative week. Less commonly, there may be a period during which the patient becomes afebrile followed by new fever 2 to 3 weeks postoperatively.[31] The fever is usually between 38 to 39°C orally but may spike as high as 40°C, particularly in children. Lack of agreement regarding other symptoms may explain the variability in incidence between centers.[1–3,8–17] Young children frequently display vague symptoms of malaise, decreased appetite, irritability, and nonspecific chest pain.[11,31,32] In older children and adults, chest pain is a more frequent complaint and includes a tightness in the chest intensified by activity or deep breathing.[11,14,31,32] The pain also may be a more typical pericardial sharp pain radiating to the neck, shoulder, or back, intensified by lying down or swallowing.[14,33] Symptoms of pleuritic pain and arthralgias also may accompany this syndrome.[14,33]

Many patients do not appear particularly ill, but a few can look extremely compromised due to high fever or pericardial tamponade. Other common physical findings include a relative tachycardia, pericardial and/or pleural friction rubs, and evidence of fluid retention such as nonspecific weight gain or hepatic congestion.[11,14,31–33] A pericardial friction rub typical of pericarditis can be heard in most patients at some time during the course of their PPS (see Chapter 92 on pericardial disease). However, the absence or disappearance of the pericardial rub must be taken in the context of clinical progress. It may reflect either healing or an enlarging effusion that separates the epicardium and pericardium throughout the cardiac cycle. Although relatively rare, a few patients progress to pericardial tamponade due to significant pericardial effusions compromising cardiac filling and output. They demonstrate tachycardia, weak thready pulses, shortness of breath, jugular venous distension, hepatomegaly, and other evidence of tamponade as previously described (see pericardial diseases). Pleural friction rubs may be accompanied by dullness to percussion and decreased breath sounds in the area if the effusion is large. The pleural effusion associated with PPS is more frequently noted on the left side.[31]

Findings in the blood may include nonspecific inflammation with a neutrophilic leukocytosis (10,000 to 30,000 WBC per cubic mm) and an elevated sedimentation rate and C-reactive protein.[17] The electrocardiogram may or may not be helpful in children with PPS. Digitalis effect and surgical right bundle branch block frequently mask the subtle electrocardiographic changes related to pericardial irritation. Potential electrocardiographic changes include ST-segment elevation and T-wave flattening or inversion in the limb leads and lateral precordial leads beyond the first postoperative week.[8–10,14,15,31]

Radiographic findings typical of pericardial effusion frequently are seen with PPS. Early or mild changes of cardiac enlargement and increased pulmonary vascularity may be difficult to separate from postoperative congestion. A large pericardial effusion is associated with an impressive enlargement of the cardiac silhouette and widening of the upper mediastinum (see Chapter 92 on pericardial disease). Patients with PPS frequently develop associated pleural effusions that can also be identified radiographically.

Echocardiography has become the hallmark of diagnosis of the pericardial effusion that is invariably present with PPS. Typically, the effusion can be demonstrated by both M-mode and two-dimensional echocardiography. Small effusions separate the epicardium and pericardium posteriorly only during systole, whereas larger effusions cause a separation of these membranes throughout the cardiac cycle and may extend anteriorly.[34,35]

In our experience, pericardial effusion is common postoperatively.[11] We studied 40 children following open heart surgery for congenital heart disease and found an effusion by echocardiographic studies in 21 (53%). In 15 of these patients, effusion was present by the second postoperative day. In general, these effusions were not large; the maximum separation of epicardium and pericardium in 17 of the patients was less than 10 mm in systole. In this study, 18 patients were diagnosed clinically to have PPS, and 16 of these had pericardial effusion. Once present, the effusion

persisted throughout the course of the clinical illness and disappeared as symptoms resolved. The 2 patients who clinically had PPS without effusion had operations with a complicated postoperative course and likely had congestive heart failure instead. Five patients had pericardial effusion without other evidence of PPS. We found echocardiography to be a good screening tool for determining those patients most likely to develop PPS.[11]

Others have found also that pericardial effusion is common postoperatively. Stevenson, et al.[36] studied 39 adult patients postoperatively and found moderate to large effusions in 22 (56%) between postoperative day 4 to 10. In another study of 122 adult patients undergoing cardiac surgery, Weitzman, et al.[37] found that 85% developed postoperative effusions; in 73% of those patients, it was present by the second postoperative day. As in our study, virtually all effusions were present by postoperative day 5, and the vast majority had reached their maximum size by postoperative day 10.[11,37] These authors found that the effusions were echo-free early but frequently developed some degree of echo-density as they peaked in size, suggesting the presence of clotted blood or exudative debris in the pericardium.[37–39] No attempt was made in this particular study to correlate pericardial effusion with symptoms of PPS. However, in our study and in Stevenson's there were a number of patients with pericardial effusion who were not symptomatic. This finding, and the higher incidence of pericardial effusion than PPS, suggests that the presence of pericardial effusion alone is not diagnostic for PPS.[11,36,37] While the presence of a pericardial effusion does not confirm PPS, we do perform an echocardiogram on all postoperative patients within 72 hours of discharge as a screening tool for those most likely to develop PPS and as a postoperative discharge baseline of cardiac function and physiologic repair.

Although PPS and postoperative pericardial effusions are common, cardiac tamponade related to late postoperative pericardial effusion is rare. Of our 40 patients, none had late tamponade, nor did Stevenson's 39 adult patients.[11,36] Weitzman reported only 1 patient with tamponade (day 3) in his 103 patients with postoperative effusion.[37] Others have reported an incidence of late tamponade (after day 7) of 0.1 to 6%, usually in patients requiring anticoagulant therapy,[40–42] and possibly unrelated to PPS.

Constrictive pericarditis does occur late postoperatively in 0.2% of patients,[43] but this does not appear to be related to PPS. None of Engle's 400 pediatric patients developed this complication. She noted that the pericardium in patients who had had PPS did not differ from those of non-PPS patients when examined at subsequent surgery.[9] In a report of 12 patients with constrictive pericarditis postoperatively, Ng, et al.[44] suspected that PPS was an etiologic factor in 4 patients who had PPS following their original surgery. However, a direct relationship was not documented. The high incidence of PPS and extremely low incidence of postoperative constrictive pericarditis makes a direct association of these two postoperative complications unlikely.

While evaluating for PPS, the clinician must remember other causes of postoperative fever and malaise. In a study of 159 adult patients febrile after postoperative day 6, Levelli, et al.[12] found that 35 of those patients had an infectious cause, and another 6 had drug-related fever. Evaluation of prolonged postoperative fever should include blood cultures to rule out endocarditis, chest x ray to assess for pneumonia and atelectasis, and careful evaluation of urine, sputum, and all wounds for signs of infection. Complete blood count, sedimentation rate, C-reactive protein, and echocardiography should be performed simultaneously to assess for PPS and other inflammatory processes. In addition, congestive heart failure must be considered because it can mimic PPS in patients with postoperative malaise, tachycardia, fluid retention, and pleural and pericardial effusions. In some patients, it is impossible to separate congestive heart failure from PPS; these patients may, in fact, have both illnesses. Only after more serious problems of infection and congestive heart failure have been ruled out or treated should the diagnosis of PPS be considered.

Treatment

Postpericardiotomy syndrome is usually a relatively benign, self-limited illness. Its very nature and the subjectivity of symptoms make assessment of therapy difficult. Frequently, only supportive therapy is necessary as the healing process continues. Bed rest has been recommended by some until the fever and pericardial effusion have disappeared.[14] Others have found no difference in duration or progression of symptoms with ambulation and recommend bed rest only if the pericardial effusion is large.[9,45] Diuretics (furosemide) are indicated for symptoms of fluid retention and for pleural and pericardial effusions.[45]

Various anti-inflammatory agents have been used for patients with PPS with symptomatic improvement. Salicylates are administered commonly in children and adults in anti-inflammatory doses (30 to 75 mg/kg/day) for 4 to 6 weeks.[14,24,33,45] Indomethacin has been shown to shorten the duration of postoperative fever and associated symptoms in adults;[12] it has not been evaluated thoroughly in children.

Steroids frequently are recommended for patients with more severe cases of PPS and large pericardial effusions.[14,31,33,45–47] In a double blind study, 12 patients who had severe PPS with elevated antiheart antibodies received either salicylates for several weeks or prednisone 2 mg/kg for the first week, 1 mg/kg for the second week, and 0.5 mg/kg for the third week.[46] The 6 patients who received salicylates soon became afebrile and improved gradually. The 6 in the prednisone group had more impressive responses with prompt resolution of clinical symptoms and findings. Antiheart antibodies in the salicylate group were not altered, whereas in the steroid group the antiheart antibodies dropped to intermediate levels and disappeared earlier than expected.[47] However, caution is recommended in the use of steroids due both to the potential for relapse and their immunosuppressive effect with regard to possible intercurrent infection.[14,47]

In a few patients who develop large or rapidly increasing pericardial effusions, supportive therapy and medications alone may not prevent compromise in cardiac output. As with other etiologies of tamponade, pericardiocentesis can be life-saving (see Chapter 92 on pericardial disease). Once stabilized hemodynamically, these patients usually respond to steroids and other supportive measures. A few may require open pericardial drainage in the form of a pericardial window related to continued compromise of cardiac output. At least one patient has been described who had four relapses of PPS with tamponade requiring repeated pericardiocenteses and three courses of steroids. This patient had total resolution of symptoms only after pericardiectomy.[48] However, the majority of patients with PPS—even those with large effusions—will respond to bed rest, diuretics, and anti-inflammatory agents without the need of surgical intervention. Because recur-

rences and late complications are rare, the overall prognosis remains excellent.

POSTPERFUSION SYNDROME

The postperfusion syndrome is a febrile illness with atypical lymphocytosis and splenomegaly. It typically occurs 3 to 6 weeks after cardiovascular surgery requiring extracorporeal circulation. Due to its late appearance, most patients have been discharged at the time the syndrome occurs. Frequently, the patient is not symptomatic and the illness is discovered at the time of routine postoperative evaluation. The fever is usually low grade at 38° to 39°C and may be accompanied by decreased appetite and vague malaise. In most patients, symptoms are mild, of short duration and do not require readmission to the hospital. The splenomegaly may last up to 3 to 4 months.

Battle and Hewlett[48] first noted this illness in 1958 when they observed the presence of atypical lymphocytes in the peripheral blood smears of five asymptomatic patients who had undergone cardiac operation requiring extracorporeal circulation. The atypical lymphocytes were thought to be similar to the Downey type I and II cells of infectious mononucleosis.[46] Others expanded and clarified the findings of postperfusion syndrome over the next several years to include the triad of fever, splenomegaly, and atypical lymphocytosis after operation, with variable additional findings of hepatomegaly, transient abnormalities of liver function, leukocytosis, hematuria, and albuminuria.[49–57] Eosinophilia, transient maculopapular rash, and adenopathy also have been reported.[52,55,57]

The incidence of postperfusion syndrome is 3 to 8% in most series.[50,51,53–55] Atypical lymphocytes usually are present in the peripheral blood smear at the time of onset of fever. The total leukocyte count is usually normal or only mildly elevated, with lymphocytosis being 25 to 85%. The atypical lymphocytes peak in 1 to 3 weeks and disappear over 1 to 3 months with their actual number ranging from 2 to 19%.[50,51,54–56]

Originally, the etiology of postperfusion syndrome was unclear, but seasonal occurence and many features of the illness suggested a viral etiology.[51,54] Subsequent studies confirmed that cytomegalovirus present in fresh blood used for the extracorporeal circulation or subsequent transfusions allowed transfer of viremia from donor to recipient.[58] This illness has now virtually disappeared with newer techniques for obtaining blood from one to several days before operation.

The diagnosis of postperfusion syndrome can be confirmed by demonstration of cytomegalovirus in the urine and by a changing titer (over several weeks) for the virus in serum. The importance of this benign syndrome is in its differentiation from more serious forms of infection such as endocarditis, wound infection, and pneumonia. An awareness of its typical features in the setting of those rare patients who receive fresh blood during or following operation should make the diagnosis clear. Treatment is symptomatic.

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CHAPTER 94

Pediatric Acquired Immune Deficiency Syndrome

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William T Shearer

The acquired immune deficiency syndrome (AIDS), first reported in the literature in a small number of homosexual adults in 1981,[1] has now expanded to affect over 30,000 individuals including children, heterosexuals and intravenous drug abusers. Over 400 children have been afflicted with AIDS and reported to the Centers for Disease Control (CDC), which estimates that these numbers will continue to increase.[2] Children with congenital heart disease may be at risk for pediatric AIDS if they received contaminated blood products prior to the currently implemented blood screening tests that became available nationwide in June 1985. Evidence for cardiac involvement in pediatric AIDS recently has been described. The pediatric cardiologist may be asked to define this involvement in affected children. This chapter gives pertinent information about AIDS in children—that is, etiologic agent, definition and diagnosis, and the implications of this infection in the care of children.

DIAGNOSIS OF AIDS

The CDC has proposed guidelines for the diagnosis of AIDS in children. Pediatric AIDS is defined as a reliably diagnosed disease at least moderately indicative of underlying cellular immunodeficiency, with no known cause of underlying cellular immunodeficiency or any other reduced resistance reported associated with that disease.[3] Those diseases accepted as indicative of underlying cellular immunodeficiency are similar to those listed for adults with AIDS: *Pneumocystis carinii* pneumonia, protracted cryptosporidiosis, atypical mycobacterial infection, and cryptococcal infection. Excluded from this list are congenital infections—specifically, toxoplasmosis or herpes simplex virus infection in the first month after birth or cytomegalovirus infection in the first 6 months after birth. In addition to congenital infections, other excluded conditions are primary immunodeficiency disorders (severe combined immunodeficiency, DiGeorge syndrome, and so on) and known pre-existing secondary immunodeficiency states (i.e., those associated with immunosuppressive therapy or lymphoreticular malignancy). A third criterion for the definition of pediatric AIDS was appended in 1985: histologic evidence of chronic lymphoid interstitial pneumonitis in a child (under 13 years) even if opportunistic disease is absent (as long as the patient has a positive test for human immunodeficiency virus [HIV]).[4] A more detailed classification of HIV infection and its clinical manifestations can be found in a recent CDC publication.[5]

ETIOLOGY

Through the work of separate investigators, the virus responsible for AIDS has been isolated and its genetic mapping elucidated. Montagnier at the Pasteur Institute and Gallo at the National Cancer Institute described LAV (lymphadenopathy-associated virus) and HTLV-III (human T cell lymphotropic virus type-III), respectively.[6,7] Subsequently, these have been identified as the same virus and are now referred to as human immunodeficiency virus (HIV)[8] (Fig. 94–1).

HIV belongs to the family of retroviruses that were first described about 50 years ago. HIV is an RNA virus that acts as an infectious agent in humans by penetrating cell membranes and utilizing the enzyme reverse transcriptase, which is carried in its core to become integrated into the cell's DNA. Genetic mapping of HIV has identified gag, pol, and env genes that are common

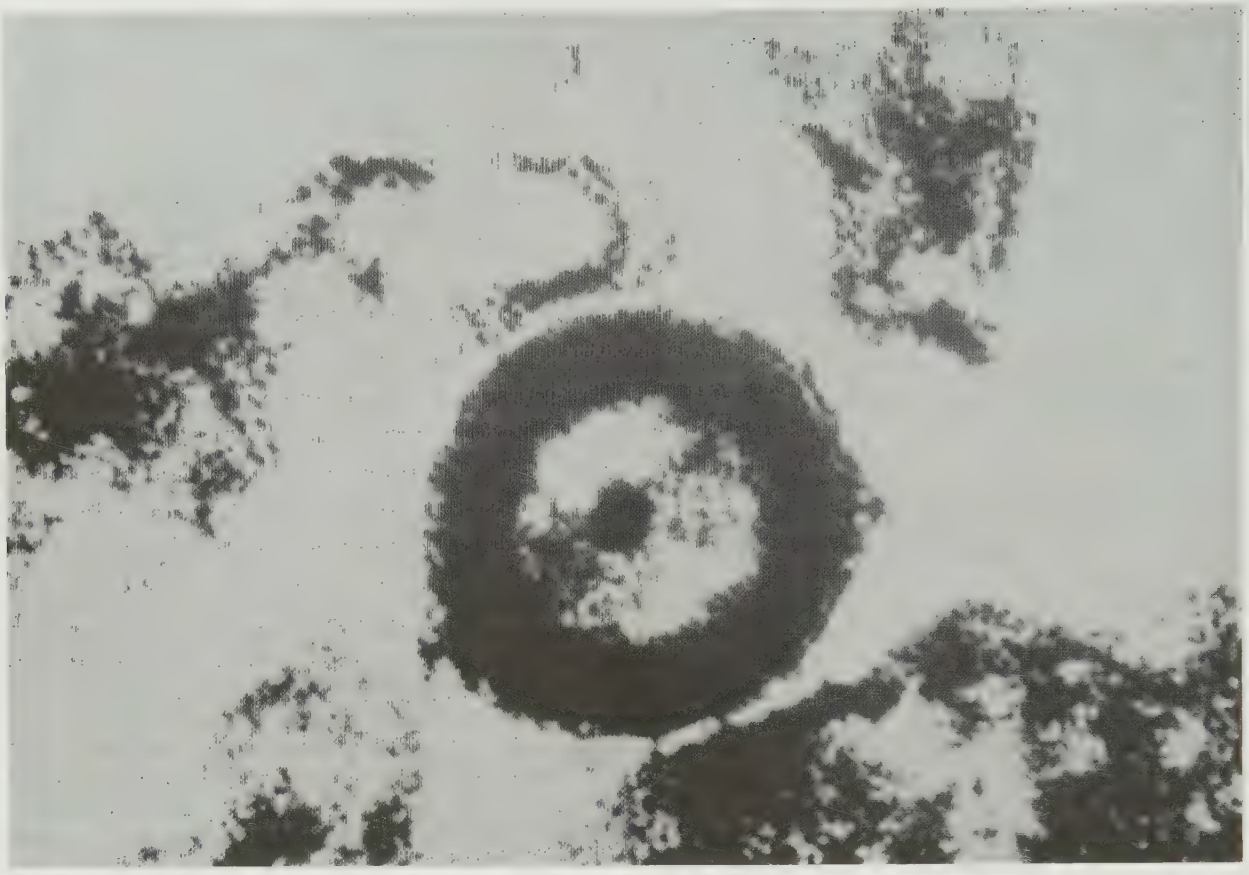

Fig. 94–1. Electron microscopic composite of HIV. (From Gallo, R.C., and Wong-Staal, R., A human T-lymphocytic retrovirus (HTLV-III) as the cause of the acquired immunodeficiency syndrome. Ann. Intern. Med., *103*:679, 1985)

to the human retroviruses and necessary for their replication[9] (Fig. 94–2). Considerable heterogeneity of the env gene and polymorphism have been noted in various HIV isolates, making preparation of an effective vaccine difficult.[10]

Continued research has led investigators to liken the HIV genome to that of Visna, a Lentivirus that infects sheep and, like HIV, has tropism for lymphocytes and central nervous tissue.[11] Although HIV has been isolated repeatedly from affected AIDS patients and those with AIDS-related complex (ARC), to date infection with the virus has not induced clinical AIDS in any animal model. Commercially available serologic tests measure human antibody response to the antigens of HIV.[9] The envelope proteins are those with the greatest immunogenicity and, as would be expected, antibodies to these antigens are most commonly encountered in patients with AIDS.[12]

EPIDEMIOLOGY

Epidemiologists have successfully assigned risk factors to greater than 95% of all reported AIDS cases (Table 94–1). Risk groups have included homosexual and/or bisexual men, intravenous drug abusers, Haitians, recipients of contaminated blood products (including hemophiliacs), heterosexuals (sexual partners of infected individuals), and children via perinatal transmission. Those children at risk for pediatric AIDS comprise three groups: Group I, children born to mothers infected with HIV (prostitutes, IV drug abusers, women with infected sexual partners, and so on); Group II, children who received HIV-contaminated blood products; and Group III, children who have been sexually abused by infected individuals (Table 94–2). Thus, researchers have concluded that HIV is transmitted by blood and intimate sexual contact.

Over 70% of all reported pediatric AIDS cases are acquired by perinatal transmission (i.e., in utero, during labor, or possibly shortly after birth).[13] In a study of more than 200 children, the age of onset of symptoms and diagnosis ranged from 1 month to 7 years (mean 17 months).[14] Evidence for prenatal transmission has been established with documentation of fetal and placental tissue infection with HIV being made as early as the middle of the first trimester.[15] The precise incidence of perinatal transmission of HIV is not yet defined although it has been estimated as high as 60 to 75%. An HIV-associated embryopathy considered to be

Table 94–1. Risk Factors in Reported AIDS Cases

Sexually active homosexual or bisexual men	65%
IV drug abusers	17%
Homosexual and bisexual IV drug abusers	8%
Transfusions of contaminated blood	2%
Hemophiliacs receiving contaminated blood factors	1%
Heterosexual activity	4%
Perinatal transmission	1%
Total	98%

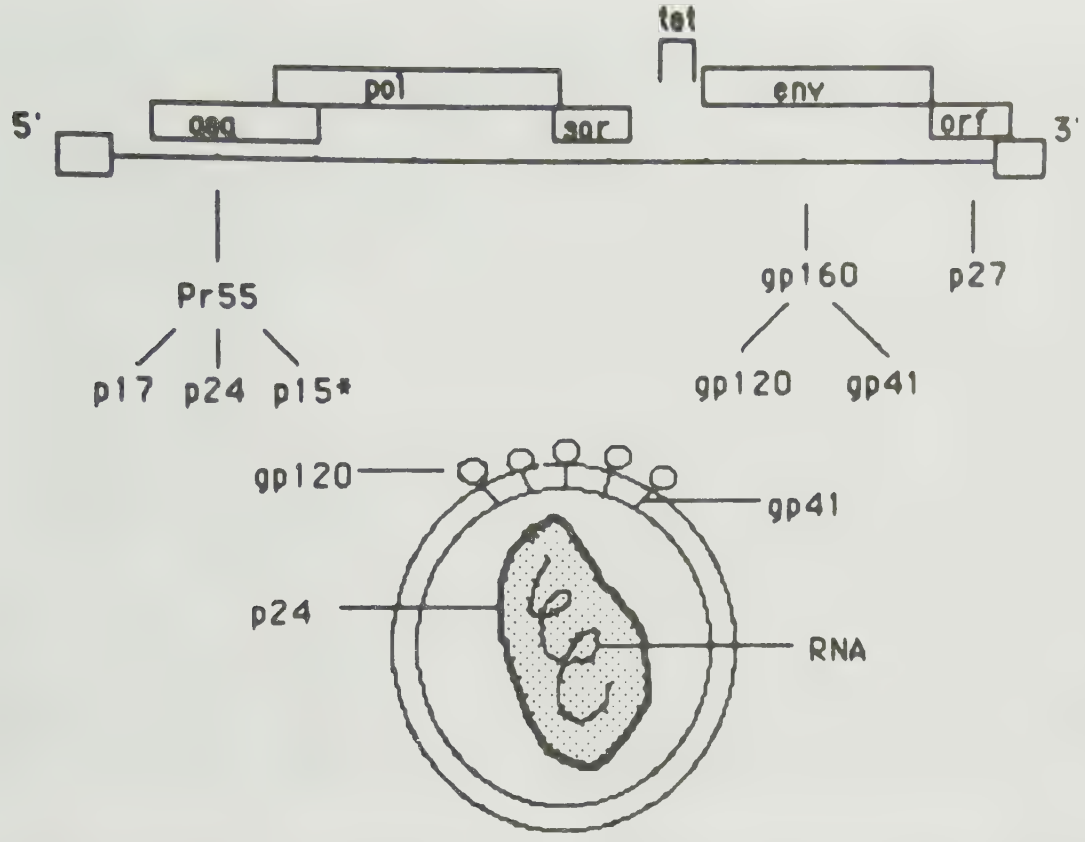

Fig. 94–2. HIV genome and translational products. The proviral genome is depicted with boxes representing known and deduced viral genes. The asterisk marks putative gene products. (From Essex, M., et al., Antigens of human T-lymphotropic virus type III/lymphadenopathy-associated virus. Ann. Intern. Med., *103*:700, 1985.)

distinct from fetal alcohol syndrome has been reported in the literature in a small number of these children.[16] Associated physical findings in HIV-associated embryopathy include growth failure, hypertelorism, boxlike forehead, flat nasal bridge, patulous lips, and microcephaly. These children are at risk for development of AIDS cardiac involvement. Additionally, fetal and postnatal morbidity appers to be increased for infants of mothers with evidence of infection (i.e., seropositive mothers),[17] compared to the general population.

The incubation period for HIV infection appears to be long. Adults with transfusion-associated AIDS have reported onset of symptoms following transfusion to range from 1 month to 5 years, with a mean of 28 months. In contrast, the range for children in a small study (12 children) was shorter, 1 month to 2½ years, with a mean of 8 months.[18] The onset of nationwide screening of blood products for HIV should significantly reduce and almost abolish this route of infection. Although Group III defines a small number of children who have been sexually abused, this possibility cannot be ignored.

Table 94–2. Children at Risk for AIDS

Infants of mothers infected with HIV through bisexual partners, prostitution, IV drug abuse
Children receiving contaminated blood or blood products
Children sexually abused by individuals with behavior at risk for HIV infection

PATHOPHYSIOLOGY

The immunopathogenesis of AIDS is not completely defined but major advances occurred following the discovery of HIV, the etiologic agent. The majority of individuals infected with HIV do not develop AIDS[5] and the incubation period for those who do develop the syndrome can be quite prolonged. Host factors appear to play an important role in determining who develops AIDS. Implicated host factors include pre-existing immune dysfunction and exposure to many antigenic stimuli either by repeated infections or foreign products (i.e., homosexuals, IV drug abusers, neonates, and hemophiliacs).

In adults with AIDS, lymphotropism has been suggested by the associated lymphopenia and decrease in the CD4 helper/inducer subset[19,20] (Fig. 94–3). Children with AIDS are less frequently noted to have absolute lymphopenia but do have selective helper/inducer depression.[21] With this prominent cytopathic effect on CD4+ (previously known as T4+) cells, presumed tropism can be at least partially explained by binding of the viral envelope protein of HIV to the CD4 molecule itself. In fact, experiments using monoclonal antibody to CD4 following incubation with HIV show effective reduction in infectivity, suggesting that the CD4 surface antigen may be a component of the viral receptor.[22] Selective depletion of this helper cell effectively modulates the immune response by decreasing production of the lymphokine, interleukin-2, by decreasing the immune response to soluble antigens, by suppressing mixed lymphocyte reactivity, and by depressing

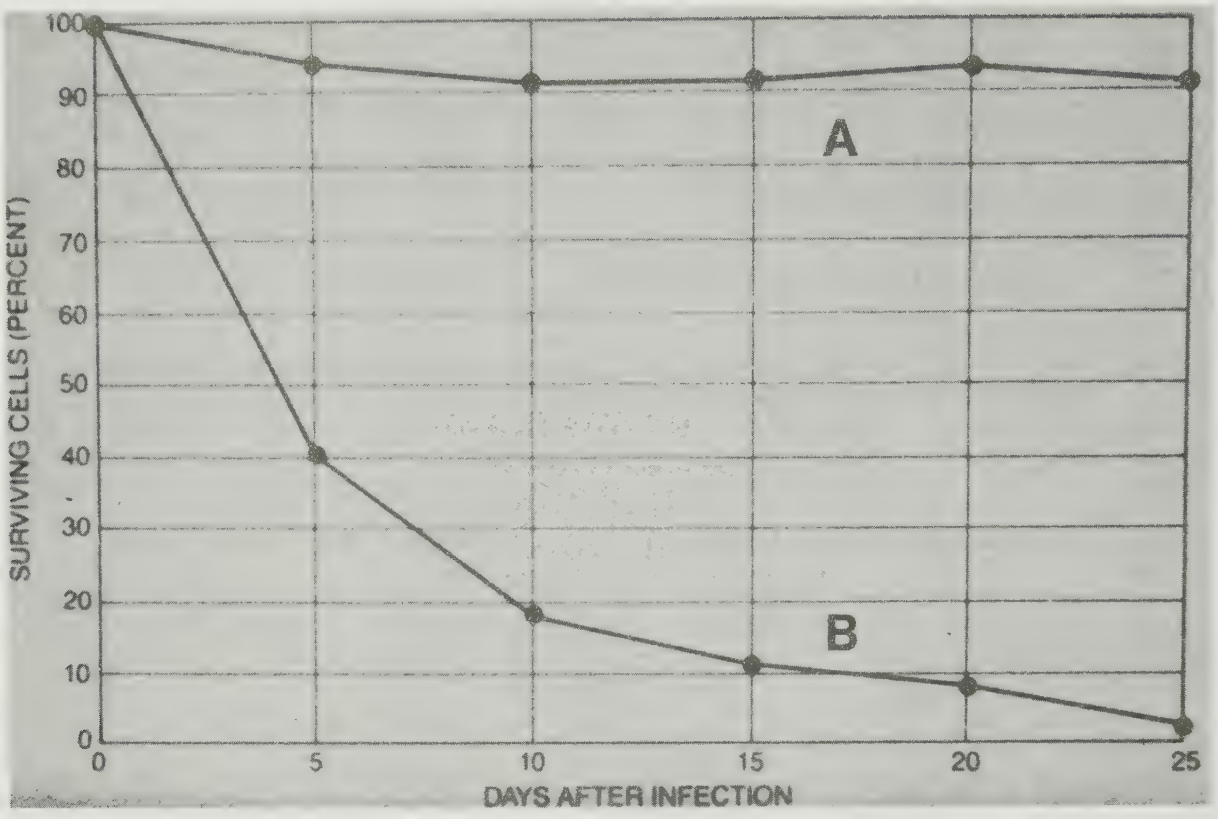

Fig. 94–3. Cell survival in culture after exposure to the AIDS virus differs by cell type. Little effect is noted on the number of CD8+ cells (A) but the number of CD4+ cells declines dramatically (B). (From Laurence, J., The immune system in AIDS. Sci. Am., *253*:84, October 1985.)

the clonal expansion of lymphocytes. In contrast to other viral infections such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV), clonal expansion of CD8+ (previously known as T8+) suppressor/cytotoxic cells is infrequently noted in HIV infection. Thus, an inverted CD4/CD8 ratio characteristic for AIDS is produced by selective depletion of the number of CD4+ helper cells, rather than by an elevation of the number of CD8+ suppressor cells. In addition, suppressor cell function is known to be defective in AIDS patients.

Other cells are affected by HIV in AIDS. For example, in children it appears that the earliest immunologic manifestation of infection involves B lymphocytes with polyclonal stimulation and increased serum immunoglobulins.[23] IgG and IgD are consistently elevated (these elevations are often 4 to 5 times normal for age). IgA and IgM also are elevated frequently. Despite hypergammaglobulinemia, functional B cell defects are noted in some patients, with absence of response to de novo challenge (i.e., absent response to protein and polysaccharide challenge). Clinically, this B lymphocyte defect is manifested by recurrent pyogenic infections, particularly bacteremia. Natural killer cell defects and functional abnormalities of monocytes also have been described in AIDS.

HIV has been isolated in the cerebrospinal fluid, brain, spinal cord, and peripheral nerve of infected patients, suggesting neurotropism[24] in addition to lymphotropism. Several distinct neurologic syndromes have been described in adults with AIDS including chronic meningitis, dementia, and AIDS encephalopathy. In children, progressive encephalopathy with loss of motor milestones and evidence of cortical atrophy on computed tomographic scanning has been described. The pathogenesis of this encephalopathy is purported to include persistent viral infection of the brain, specifically HIV infection.[25] More recent investigations have described HIV isolation from monocytoid cells in the brain tissue of AIDS patients with encephalopathy, lending further credence to neurotropism and the important role of infection of monocyte/macrophages in this syndrome.[26,27]

CLINICAL MANIFESTATIONS

Pediatric AIDS differs clinically from the syndrome described in adults. The most distinct differences are the infrequent finding of lymphopenia or Kaposi's sarcoma in affected children. To date, only two children have been described in the literature with Kaposi's sarcoma.[28] This differs distinctly from adults who present with Kaposi's sarcoma alone or in conjunction with opportunistic infection in greater than 33% of reported cases.[20]

The typical clinical presentation of pediatric AIDS frequently is not clearly distinguishable from other chronic diseases (i.e., cystic fibrosis, primary immunodeficiencies, malnutrition, Crohn's disease, etc.).[23,29] Salient clinical features include failure to thrive, chronic interstitial pneumonitis, hepatosplenomegaly, diffuse lymphadenopathy, protracted diarrhea, salivary gland enlargement, thrombocytopenia, and recurrent otitis[21,23] (Table 94–3). Chronic interstitial pneumonitis has been described in almost 100% of affected children and histologic evidence of lymphoid interstitial pneumonitis (LIP) is a definitive diagnostic criterion of AIDS in children. Attempts to distinguish LIP clinically

Table 94–3. Clinical Manifestations of Pediatric AIDS*

Chronic interstitial pneumonitis	100%
Hepatosplenomegaly	97%
Failure to thrive	94%
Diffuse adenopathy	56%
Protracted diarrhea	39%
Thrombocytopenia	31%
Eczemoid rash	19%
Recurrent otitis media	19%

*Modified from Shannon, K.M. and Ammann, A.J., Acquired immune deficiency syndrome in children. J. Ped., *106*(2):332, 1985.

from *Pneumocystis carinii* pneumonia have included noting a more severe hypoxemia and a higher serum lactate dehydrogenase level in children with *Pneumocystis* pneumonia.[30] In LIP, serologic assays of lung tissue and blood suggest persistent EBV infection. At present, distinction of these two pulmonary diseases in AIDS children is only possible histologically. Chronic interstitial pneumonitis in pediatric AIDS may be confused with interstitial pulmonary edema. Neurologic manifestations have been described in children including progressive encephalopathy, ataxia, and isolated seizures.[25]

The opportunistic infections of pediatric AIDS are not dissimilar from those described in adults, with the exception of exclusion of congenital viral infections (i.e., congenital Herpes simplex, toxoplasmosis or CMV in the first 6 months of life). Associated infections in children have included those due to *Candida* species, *Pneumocystis carinii*, EBV, CMV, gram negative bacteria, *Staph aureus* and *Strep pneumoniae*[21] (Table 94–4). *Pneumocystis carinii* pneumonia along with LIP are the two most common pulmonary diseases in pediatric AIDS. *Pneumocystis* pneumonia is, in fact, the most common infection in pediatric AIDS and is described in 70% of children reported to the CDC.[19] Atypical mycobacterial infections (particularly those due to *M. avium-intracellulare*) were noted in one center's study to affect 8% of children with AIDS under 3 years of age. The incidence increased in older children and in those with progressive decline in immunologic function.[23] Oral thrush is a common finding in infants with AIDS; more severe candidal infections have included sepsis, central nervous system involvement, and esophagitis. Other fungal infections described in pediatric AIDS patients include *Cryptococcus neoformans* (meningitis and disseminated disease) and disseminated Histoplasmosis.[23] CMV infections are considered opportunistic infections in pediatric AIDS when infection is documented outside of lymph node or liver tissue. Clinically, CMV infections have been described in pediatric AIDS in the form of pneumonia and meningitis. Bacterial infections are common and the incidence of sepsis high in children with AIDS. In one study, over 50% of evaluated children with AIDS were reported to be septic; the most common bacterial pathogen was identified as *Streptococcus pneumoniae*.[23]

Laboratory findings in pediatric AIDS include a selective CD4 helper/inducer lymphopenia (absolute lymphocyte count may remain normal), an inversion of CD4/CD8 ratio, and an abnormal lymphocyte function with depressed in vitro responses to mitogens (phytohemagglutinin, concanavalin A) and anergy to delayed hypersensitivity skin test[31] (Table 94–5). Hypergammaglobulinemia is a frequent finding and has been associated in a small number of AIDS patients with IgG subclass deficiencies. The response of B cells to de novo antigen challenge has been abnormal in some AIDS patients, with no rise in serologic titers following immunization with diphtheria, tetanus, and so on. Anemia (frequently Coombs positive) and thrombocytopenia have been described. Serologic testing for HIV is almost always positive both by the screening test (ELISA) and the more specific confirmatory test (Western Blot). The chest radiography typically defines evidence of chronic pulmonary disease with hilar prominence and, often, diffuse interstitial or nodular infiltrates (Fig. 94–4).

Table 94–4. Opportunistic Infections in Pediatric AIDS*

Pneumocystis carinii pneumonia
Candidiasis—esophagitis, meningitis, sepsis
Mycobacterium avium—pneumonia, hepatitis, disseminated
Cytomegalovirus—pneumonia, central nervous system, gastroenteritis
Herpes Simplex (disseminated) ulcerating lesions
Cryptosporidium—enteritis
Toxoplasma gondii—central nervous system, pneumonia
Lactobacillus—sepsis
Cryptococcus neoformans—central nervous system, disseminated
Histoplasmosis (disseminated)
Strongyloidosis—pneumonia, central nervous system, disseminated

*Taken with permission from Rubinstein, A., Pediatric AIDS. *In* Current Problems in Pediatrics. Chicago, Year Book Medical Publishers, 1986, p. 363.

CARDIAC COMPLICATIONS

In 1984, the first evidence for cardiac abnormalities in adults with AIDS was reported.[32] Seventy-three percent of the patients evaluated in this study were noted to have cardiac abnormalities, including pericardial effusions (some resulting in cardiac tamponade), increased right ventricular size, and mitral regurgitation (Fig. 94–5). Subsequent studies have described nonbacterial thrombotic endocarditis with embolization to major organs and congestive cardiomyopathy in adults with AIDS.[33,34] Other pathologic findings in adults have included metastatic Kaposi's sarcoma, *Cryptococcus neoformans* myocarditis, and cardiac aspergillosis.[35–38]

Evidence for cardiac involvement in pediatric AIDS has been described and was noted in as many as 63% of patients evaluated.[39] Echocardiographic abnormalities included pericardial effusion and left ventricular dilation with decreased contractility. Left ventricular dysfunction was noted to be the most frequent echocardiographic abnormality.[40] Right ventricular dysfunction is described in association with left ventricular abnormalities and is suggested to be the result of repeated or chronic lung disease,[41] with presumed pulmonary hypertension. Electrocardiographic changes also were frequently noted, including ventricular hypertrophy and complete

Table 94–5. Immunologic Abnormalities in Children with AIDS*

Hypergammaglobulinemia	93%
Decreased lymphoproliferative responses	80%
Reversed CD4/CD8 ratio	78%
CD4 lymphopenia	41%
Hypogammaglobulinemia	3%
Absolute lymphopenia	3%

*Modified with permission from Pahwa, S., et al., Spectrum of human T-cell lymphotropic virus type III infection in children. JAMA, *255*(17):2299, 1986.

Fig. 94–4. Chest radiograph of an infant with AIDS with pulmonary lymphoid follicular hyperplasia. Marked hilar lymphadenopathy and interstitial infiltrates completely obscure the heart borders.

Fig. 94–5. Two dimensional echocardiogram in AIDS. (A) Long axis view. (B) Short axis view. (C) Apical 4-chamber view. Black arrows point to large pericardial effusion (PE). White arrows indicate right atrial (RA) collapse consistent with cardiac tamponade. AO = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle. (From Fink, L., Reichek, N., and St. John Sutton, M.G., Cardiac abnormalities in acquired immune deficiency syndrome. Am. J. Cardiol., *54*:1161, 1984.)

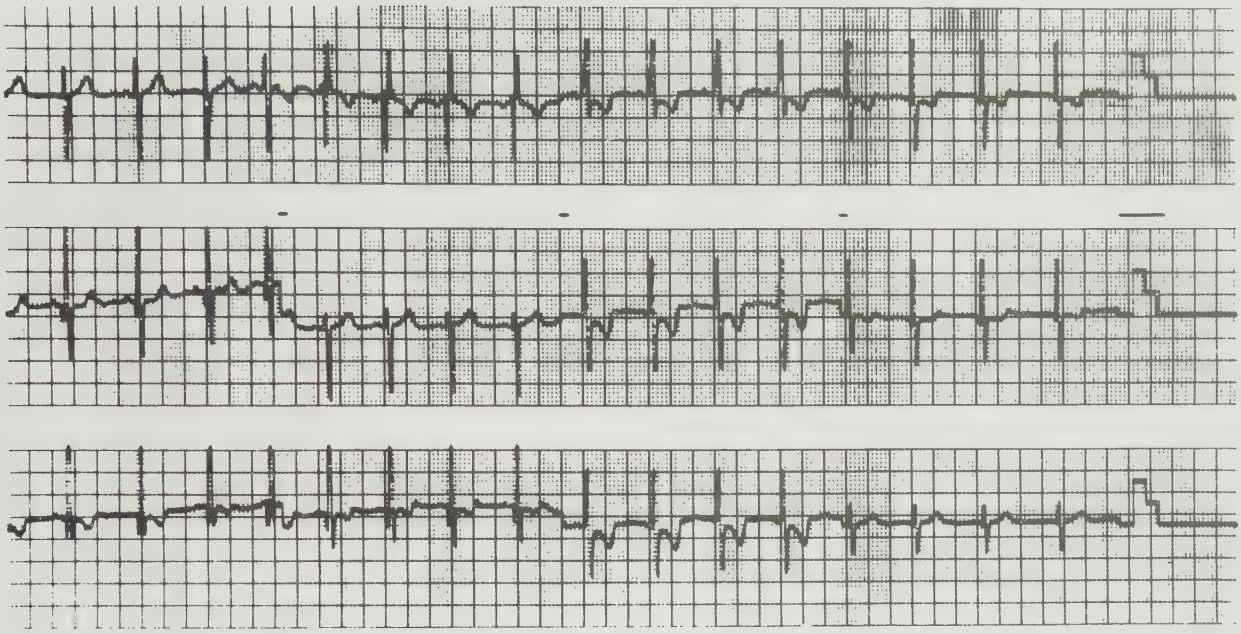

Fig. 94–6. ECG at the time of exacerbation of cardiac failure in a child with AIDS demonstrating right axis deviation and marked right ventricular hypertrophy. (From Steinherz, L.J., Brockstein, J.A., and Robins, J., Cardiac involvement in congenital acquired immunodeficiency syndrome. Am. J. Dis. Child., *140*:1241, 1986.)

right bundle branch block (Fig. 94–6). There are, as yet, no reported cases of cardiac malignancy or nonbacterial thrombotic endocarditis in pediatric AIDS.

DIFFERENTIAL DIAGNOSIS

The salient clinical features of pediatric AIDS are noted frequently in many other chronic pediatric diseases. Hence, the differential can be lengthy and include other causes of secondary immunodeficiencies including severe malnutrition, immunologic decline following immunosuppressive therapy, and other viral infections (EBV, CMV).

Remarkable hypergammaglobulinemia is a consistent finding in pediatric AIDS and may help to distinguish AIDS from other early viral infections in children. The selective CD4 lymphopenia and resultant inverted CD4/CD8 ratio also may help to distinguish HIV infection from other viral infections.

Since the discovery of HIV as the etiologic agent of AIDS, serologic assays for HIV have been particularly helpful in piecing together what can present a most confusing puzzle to clinicians. The ELISA (enzyme linked immunosorbent assay), first commercially available in 1985, is an effective screening test with excellent sensitivity and modest specificity for antigens of HIV.[42,43] This is the serologic assay used by blood banks nationwide for screening of blood donors. For this purpose, high sensitivity makes it a most useful tool. The reduction in specificity, on the other hand, limits its potential as a diagnostic test for AIDS, and other serologic assays with enhanced specificity to HIV are used to confirm the ELISA results. These tests include the Western Blot, the cytoplasmic immunofluorescence test, the membrane immunofluoresence test (MIF), and the highly sensitive, although not commercially available, radioimmunoprecipitation assay (RIPA).[9] It is imperative to recall that a positive AIDS test infers HIV infection but does not by itself diagnose AIDS. AIDS is diagnosed by the presence of a constellation of clinical findings of which the serologic data is only a part. The diagnosis of AIDS in adults and children is made by documentation of a T-lymphocyte defect characteristic of HIV infection with associated opportunistic infections or in children associated with chronic lymphoid interstitial pneumonitis.

Confusion results when serologic data suggest HIV infection but pertinent immunologic data is normal and there is no evidence of opportunistic infections in the patient. Therefore the CDC has classified and staged HIV infection and included AIDS as an extreme manifestation of the spectrum of this disease. Information regarding progression of quiescent HIV infection to clinical AIDS currently is not available although it is clear that this data will be forthcoming in the near future.

PRECAUTIONS FOR FAMILIES AND HEALTHCARE WORKERS

The prognosis for AIDS is as dismal in children as in adults; death occurs in over half of the children reported to the CDC. For surviving children, there is another problem with social ostracism caused by public fear and misunderstanding. In an effort to assist with these latter issues, the CDC has proposed guidelines for the schooling and foster-care placement of affected children.[44] Current information on the transmissability of HIV infection documents the *lack* of evidence for a casual transmission of HIV.[45–49] These CDC guidelines include placement of school aged children in schools (classroom, after-school daycare, and so on) and foster homes without restrictions. Re-evaluation of each child on the basis of his/her general health and risk of classroom exposure (i.e., influenza, varicella, and so on) is encouraged frequently since these infections are potentally fatal in immunocompromised

children. Informed primary caretakers are encouraged to practice good handwashing when in contact with bodily fluids of infected children. Paramount in these guidelines is the reminder that the child's right to privacy be maintained and medical records be kept confidential.

As the majority of pediatric AIDS cases (70%) are acquired by perinatal transmission, it is prudent to test other family members, especially siblings, for evidence of HIV infection. However, indiscriminate testing is not warranted and only those defined as household members at risk (sexual partners, parents as potential sources of infection, and siblings) should be screened.

Precautions for the healthcare provider dealing with AIDS patients are similar to those recommended to the healthcare provider for patients with hepatitis B infection (i.e., good handwashing with exposure to bodily fluids particularly blood).[50] Healthcare workers are often at an increased risk to bloodborne infections because of accidental percutaneous exposure to blood (i.e., needlestick injuries). Current data suggest that, even with needlestick injuries, HIV infection is difficult to acquire.[51–54] With these data in mind, guidelines for preventing transmission of HIV in the workplace have be published. Emphasis is placed on education and techniques for avoiding percutaneous puncture.[54] Further recommendations for preventing HIV infection during invasive procedures also have been outlined.[55] Eye protection and gloves for those handling a patient's blood during heart catheterization is prudent.

TREATMENT AND THE FUTURE

The current therapeutic approach to AIDS is supportive—that is, antimicrobial therapy for identified infections and nutritional support for inanition associated with infections. Experimental treatments of AIDS have included immunoreconstitution with bone marrow transplantation, immunomodulatory drugs, viral eradication with antiviral agents, and immunoglobulin replacement therapy in children.[56–58] Some of these attempts have met with failure and others with modest success. Immunoglobulin replacement has been suggested for pediatric AIDS patients, despite their elevated serum immunoglobulin levels, because of the high incidence of bacteremia and B lymphocyte functional defects noted in some infected children. Perhaps a more appropriate practice would be the treatment of only those infected children with identified functional B cell defects.

Attempts to provide a vaccine for the prevention of AIDS has been stymied by viral variability and polymorphism.[59] The advent of an effective vaccine against another retrovirus, feline leukemia virus, has been encouraging.[59] Large-scale education programs dealing with sexual education and IV drug abuse have been launched to provide information regarding transmission of HIV infection. Within the past few years, the medical community has gained an enormous amount of information regarding AIDS. It is hoped that in the future a cure will be available for this infection.

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Index

Page numbers in *italics* refer to illustrations; numbers followed by the letter "t" refer to tabular matter.

A band, 130, *131*, 212
Abbott, Maude, 1246
Abdominal binding
  in cardiopulmonary resuscitation, 422
Abetalipoproteinemia, 46, 477
Abortion(s)
  induced
    decision-making on, 2519-2520
    prenatal diagnosis and, 173
  spontaneous
    in mothers of congenital heart disease patients, 676
Abscess(es)
  cerebral. *See* Brain abscess
  dental, *2352*, 2352
  myocardial
    Staphylococcus aureus, 2469, *2470*
  pericardial
    computed tomography assessment of, *889*
Absent pulmonary valve syndrome, 1101-1107, *1102-1104*
  anomalies associated with, 1102
  congestive heart failure due to, 1102-1103, 2012
  patent ductus arteriosus vs., 1065
  pulmonary complications of, 2507, 2511
  radiographic findings in, 703, *706*
Absolute resistance unit(s), 933
Absorption
  of carbohydrates
    in heart disease, 2358
  of drugs, 471-472
    interactions involving, 473-474
  of fats
    in heart disease, 2358
  of protein
    in heart disease, 2358
Abstinence counseling, 2371-2372
Accelerated ventricular rhythm, 1876, *1879*, 1887
Accessory atrioventricular connection. *See* Kent bundle
Accuracy
  of diagnostic tests, *143*
Acebutolol
  pharmacology of, 2364t
    in hepatic, gastrointestinal or nutritional disorders, 2365
Acetaminophen
  dosage adjustment for renal insufficiency, 2440t
Acetazolamide, 2106
  dosage adjustment for renal insufficiency, 2441t
  in acute mountain sickness treatment, 446
  in high altitude pulmonary edema treatment, 445
  pharmacology of
    in hepatic, gastrointestinal or nutritional disorders, 2366
Acetylcholine
  effects on pulmonary circulation, 374t, 376
Acetylcoenzyme A (acetyl-CoA)
  formation of
    from fatty acids, 195
    from pyruvate, 193-194
  oxidation of
    in citric acid cycle, 196
Acetylene rebreathing method
  cardiac output measurement by, 832
    during exercise testing, *833*, 833
N-Acetylgalactosamine-4-sulfatase deficiency
  in Maroteaux-Lamy syndrome, 1660
Acetyl-LDL receptor, 482
Acetylsalicylic acid. *See* Aspirin
Acid
  net excretion of, 462
  sources of
    from diet and tissue constituents, 460t, 460
Acid ceramidase deficiency
  in Farber disease, 1662
Acid lipase deficiency, 1662. *See also* Cholesteryl ester storage disease
Acid maltase deficiency
  in Pompe's disease, 1664
Acid-base balance. *See also* Acidosis; Alkalosis
  drugs for use in adjustment of, 2553t
  renal regulation of, *460-461*, 460t-462t, 460-462
Acidosis. *See also* Metabolic acidosis
  avoidance of
    in pulmonary vascular disease patient, 2004
  electrocardiographic findings in, 749
  in development of cor pulmonale, 2502
  in myocardial blood flow regulation, 258
  intracellular
    in myocardial ischemia, 1689-1690, 1690-1691
  postoperative, 2253
  rewarming, 2302
Acinus
  pulmonary, *350*, 350, 360
Acoustic impedance, 525
  of various media, 525t
Acquired immune deficiency syndrome (AIDS), 1605-1613
  cardiac complications in, 1609-1611, *1610-1611*
  clinical manifestations of, 1608-1609, 1609t, *1610*
  criteria for diagnosis of, 1605
  differential diagnosis of, 1611
  epidemiology of, 1606t-1607t, 1606-1607
  etiology of, 1605-1606, *1606-1607*
  fear of
    blood transfusions and, 2260-2261
  immunologic abnormalities in, 1609t, 1609
  malignancies and
    in cardiac transplant recipients, 2247
  opportunistic infections in, 1609t, 1609
  pathophysiology of, 1607-1608, *1608*
  precautions for families and healthcare workers in, 1611-1612
  risk factors for, 1606, 1606t-1607t
  treatment of, 1612
Acrocyanosis, 672
Acromegaly, 2495
ACTH (corticotropin)
  increased production of, 2495
Actin, 37-40. *See also* Actomyosin complex
  in thin filaments, 130, *131*, *213*, 213-214, 2065-2066, *2066*
Actinomycin D
  doxorubicin cardiotoxicity and, 2339
Action potential(s), 294-299
  characteristics of, 296-299
  disease's effects on, 310
  fast response, 296-297
    depressed, 310
  heterogeneity of properties of, *296*, 296, 297t
  in embryonic heart, 309
  in neonatal heart, 309
  ionic basis of, 301-308
    in phase 0, 302-304
    in phase 1, 305
    in phase 2, 305-306
    in phase 3, 306-307
    in phase 4, 307-308
  phases of, *295-296*, 295-296
  slow response, 296-297
    calcium channels in, 304
Activated clotting time (ACT)
  heparin activity estimation with, 2300
Activation voltage, *296*, 296
Actomyosin complex. *See also* Cross-bridge(s)
  regulatory mechanisms in, 214, 215-217, *216*
Acute margin of heart, 111
Acyclovir, 2061
Acyl carnitine
  in lipid metabolism, *195*, 195
Acyl CoA dehydrogenase deficiency, 1667
Acyl-CoA derivative(s)
  formation and transport of, 194-195
Adams-Stokes syndrome, 1934
Adenine arabinoside, 2061
Adenosine
  as antiarrhythmic agent, 2552t
  in regulation of ductus arteriosus closure, 2112
  in regulation of myocardial blood flow, 258-259
  synthesis of
    in lungs, 366
Adenosine diphosphate (ADP)
  conversion of, to adenosine
    in lungs, 366
  in citric acid cycle, 196
Adenosine monophosphate (AMP)
  cyclic. *See* Cyclic adenosine monophosphate
  in RNA, 14
  removal of
    in lungs, 365-366

Adenosine triphosphate (ATP)
as antiarrhythmic agent, 2552t
cellular stores of, 428
regeneration of, 428-429
hydrolysis of, by actomyosin, *216,* 216-217
in cardiac muscle
nuclear magnetic resonance studies of, 614-615
in sodium-calcium exchange regulation, 204-205
removal of
in lungs, 365-366
stimulation of calcium release by, 206
Adenosinetriphosphatase (ATPase). *See also* Calcium adenosinetriphosphatase
contractile protein
measurement of, 217
Adenylate cyclase
control of activity of, 321-322, *322*
Adenylate cyclase agonist(s), 2068
Admittance
defined, 502
Adolescence
psychological aspects of congenital heart disease in, 2523-2526
Adrenal gland, 2494
disease of
cardiac involvement in, 2494-2495
involvement of, in acute myocardial infarction, 1696
Adrenal insufficiency
congestive heart failure due to, 2013
electrocardiographic findings in, 754
Adrenergic activity
ductus arteriosus closure and, 2110
prostaglandins and, 2111
myocardial
in heart failure, *245,* 245-246
myocardial blood flow regulation and, 259-260
Adrenergic agonist(s). *See also* Alpha-adrenergic agonist(s); Beta-adrenergic agonist(s); particular agents
mechanisms of action of, 2067-2068, 2068t
Adrenergic receptor(s), 328. *See also* Alpha-adrenergic receptor(s); Beta-adrenergic receptor(s)
inotropic agents' effects on, 2067-2068, 2068t
measurement of, 334-335
in syncope diagnosis, 1945
role of, in myocardial contraction, 2066-2067, *2067*
Adrenocorticotrophic hormone (ACTH)
increased production of, 2495
Adriamycin. *See* Doxorubicin
Adulthood
psychological aspects of congenital heart disease in, 2523-2526
Aerobic capacity, 429
Aerobic fitness
measurement of, 2269
Affirmative action
application to handicapped, 2528-2529
Afterdepolarization(s), 311
delayed
mechanisms of arrhythmias due to, 314-315, *315*
early
mechanisms of arrhythmias due to, *315,* 315-316
Afterload, 224
basic concepts of, *2087,* 2087
estimation of, 224
force development and, 224
in intact heart, 235-236
manipulation of, 2086-2098
experiences with, in children, 2089t
mechanical, *2090,* 2090-2091
pharmacologic, 2088t, 2088-2090, 2091-2096, 2549t
physiology of, 2086-2088, *2087*
postoperative, 2256
stroke volume and, 237-239, *238*
in fetus and newborn, 240, *241*
studies from isolated cardiac muscle, 234-235, *235-236*
Agarose-gel electrophoresis
in DNA analysis, 21, *23*
AIDS. *See* Acquired immune deficiency syndrome
AIDS encephalopathy, 1608
Air embolism
procedures for preventing
in pulmonary vascular disease patient, 2004
with open heart surgery, 2298
Air gap technique
in digital subtraction angiography, 638
Air travel, 448
Airway(s)
development of, 349
lining epithelium of, 350
obstruction of
cor pulmonale due to, 2503
in absent pulmonary valve syndrome, 1101
peripheral, with left-to-right shunt lesions, 2507
pulmonary edema due to, *396,* 396
postoperative care of, 2251-2255
Airway resistance, 352-353
Akinesis
defined, 839, 1694
Alagille syndrome, 2362, 2403, 2429t
Alanine
in pyruvate metabolism, 194
Albumin
in fatty acid transport, 194
lipid-free
infusion of, for myocardial protection, 270
technetium-labeled macroaggregated, 564
vascular perfusion imaging with, 847
Alcohol
atherosclerosis and, 1992
cardiotoxicity of, 1673
effects on fetus. *See* Fetal alcohol syndrome
hypoadrenergic dysautonomia due to, 340
use of, by heart disease patients, 2526
Aldactone. *See* Spironolactone
Aldomet. *See* Methyldopa
Aldosterone. *See also* Renin-angiotensin-aldosterone system
changes in
in space, 437-438
renal handling of sodium and, 458
Aldosterone antagonist(s), 2105. *See also* Spironolactone
for congestive heart failure, 2016
Aliasing
in color Doppler echocardiography, 540
in computer-processed electrocardiograms, 516, *517*
in Doppler echocardiography, 538
in nuclear magnetic resonance, 609
Alkaline phosphatase
levels of, in ischemic liver disease, 2361
Alkalosis
contraction
in diuretic therapy for congestive heart failure, 2016
induction of
in management of persistent pulmonary hypertension in neonate, 2485-2486
Alkaptonuria
molecular basis of, 47
Alkylating agent(s). *See also* particular agents
cardiotoxicity of, 2341
Allele
defined, 60
Allergy
to antibiotics, 2049
Allopurinol
effects on postischemic dysfunction, 275
Alpha emission, 561
Alpha-adrenergic agonist(s). *See also* particular agents
effects on pulmonary circulation, 373, 374t
in cardiopulmonary resuscitation, 410-413
mechanisms of action of, 320, 2067, 2068t
use of, in pregnancy, 2385
Alpha-adrenergic antagonist(s). *See also* particular agents
effects on pulmonary circulation, 373-375, 374t
Alpha-adrenergic receptor(s), *320,* 320-321
activity of, 328
evaluation of responsiveness of, 334
inotropic agents' effects on, 2067, 2068t
measurement of, 334-335
in syncope diagnosis, 1945
on ductus arteriosus, 2110
on pulmonary vessels, 362
relative potencies of agonists and antagonists at, 319t
role of, in myocardial contraction, *2067,* 2067
Alpha-1-antitrypsin
in nutritional assessment, 2356
Alphaprodine (Nisentil)
for obstetric analgesia, 2387t
Altitude, 441-449
barometric pressure and, 441-442
chronic pulmonary disease and, 447-448
congenital heart disease and, 447
diseases of, 445-446, 446t
effects on cardiovascular system, 442-443, 443t
hematologic changes with, 443-444
hemoglobinopathy and, 448
high
defined, 441
metabolic changes with, 444
of selected cities, 441t
oxygen transport changes with, 442-443, 443t
perinatal medicine at, 446-447
pulmonary edema and, 445
pulmonary hypertension and, 444-445
sensory, motor and mental function changes with, 444
Alu family, 15, 17
defined, 60
Alveolar capillary membrane, *388,* 388
in protection against pulmonary edema, *392,* 392
Alveolar hypoventilation
cor pulmonale due to, 2504
Alveolar septum, 386-388, *387-388*
Alveolar volume, 356
Alveolar-capillary barrier. *See* Alveolar capillary membrane
Alveolus(-i), *350,* 350
Amantadine hydrochloride, 2061

Amber mutation
  defined, 60
Amikacin, 2056-2057
  dosage adjustment for renal insufficiency, 2440t
  parenteral dosage for severe infection, 2057t
Amiloride, 2105
  pharmacology of
    in hepatic, gastrointestinal or nutritional disorders, 2366
Amino acid(s)
  absorption of
    in heart disease, 2358
  cellular uptake of, 198
  genetic coding for, 5, 6t
  metabolism of, 196
Aminoglycoside(s), 2056-2057. *See also* particular drugs
  digoxin interaction with, 2052
  diuretic interactions with, 2052
  dosage adjustment for renal insufficiency, 2440t
  resistance to
    mechanisms of, 2056
  synergism with other antibiotics, 2056
  toxicity of, 2049, 2057
    to kidneys, 2057, 2428
Aminophylline, 2554t
  effects on pulmonary circulation, 374t, 377
Aminorex fumarate
  effects on pulmonary circulation, 379
Aminosalicylic acid
  digoxin interaction with, 2363
Amiodarone, 2127t, 2132, 2551t
  dosage adjustment for renal insufficiency, 2441t
  drug interactions with, 2052, 2132
  effects on electrocardiogram, 751
  in atrial fibrillation treatment, 2171
  in atrial flutter treatment, 1857
  in hypertrophic cardiomyopathy management, 1633, 1893
  in ventricular arrhythmia treatment, 1899
  pharmacology of, 2364t
    in hepatic, gastrointestinal or nutritional disorders, 2366
  side effects of, 2132
    cutaneous, 2422
    hepatic and gastrointestinal, 2368
  thyroid function and, 2493-2494
  ventricular arrhythmias due to
    treatment of, 1897
Ammonia
  buffering action of, 461-462
Ammonium chloride, 2553t
Amniocentesis, 20, *21*
Amniotic cavity, 72
Amniotic fluid, 283
Amoxicillin, 2052-2053
  clavulanic acid with (Augmentin), 2053
  prophylactic dosage of, 2473
Ampere
  defined, 2152
Amphetamine(s)
  maternal use of
    congenital heart disease and, 676
Amphotericin B, 2061
  digoxin interaction with, 2052
  dosage adjustment for renal insufficiency, 2440t
  for infective endocarditis, 1572
  for posttransplant infection, 2468
Ampicillin, 2052-2053
  dosage adjustment for renal insufficiency, 2440t
  parenteral dosage for severe infection, 2057t
Amplitude
  defined, 2152
Amrinone, 2548t
  age differences in response to, 2073
  clinical use of, 2072
  in congestive heart failure management, 2018
  in idiopathic dilated cardiomyopathy management, 1623
  in myocardial infarction management, 1717
  in postoperative management, 2257
  pharmacology of, 2072
  side effects of, 2072
Amsacrine
  cardiotoxicity of, 2341
Amyl nitrate
  effects on pulmonary circulation, 374t, 377
Amyloidosis, 1671-1672, *1672*
  technetium-99m pyrophosphate scan findings in, 845
Anaerobic threshold, 429, 831-832
Analgesic(s), 2553t
  obstetric, 2387t, 2388-2389
Analog-to-digital conversion, 658
  defined, 616
  for digital subtraction angiography system, 639-640
  in computer processing of electrocardiograms, 516-517, *517*
Analysis of variance (ANOVA), 651-652
Anamnestic response, 2240
Anatomy
  cardiovascular, 109-134
    echocardiographic assessment of, 769, 777-780, *778-780*
    normal radiographic, 692-695, *693-695*
    nuclear magnetic resonance evaluation of, 853-855, *855*
    systematic approach to, 109-110, 769
Ancef. *See* Cefazolin
Andersen disease, 1665
Anemia(s)
  cardiovascular complications with, 2330-2335, 2331t
  cardiovascular effects of, 2330, 2331t, *2332*
  chronic, 1670
  Cooley's. *See* Thalassemia(s)
  defined, 2330
  due to intravascular mechanical hemolysis, 2342, *2345*, 2345
  Fanconi's, 678t, 678, 2329t, 2329
  in tetralogy of Fallot
    neurologic complications and, 1089
  in transposition of the great arteries
    neurologic complications and, 1202
  iron deficiency, 2330-2332, *2332*
  relative
    in hypoxemia, 1998
    stroke and, 2305
  sickle cell. *See* Sickle cell disease
Anesthesia, 2289-2304
  balanced, 2289
  clinical caveats for specific diseases, 2299t
  conduct of, 2297-2299
  equipment for, 2291, *2292-2293*
  evaluation before, 2290
  history of, in congenital heart disease, 2289-2290
  in pulmonary vascular disease, 2005
  in sickle cell disease, 2335
  induction of, 2297
  intraoperative complications of, 2298
  maintenance of
    for closed heart operations, 2298
    for noncardiovascular operations in congenital heart disease patients, 2298-2299
    for open heart surgery, 2297-2298
  monitoring during, 2295-2297
  obstetric, 2375, 2387t, 2388-2390
  preparation for, 2290-2293
  resuscitation drugs for use during, 2293t, 2293
  transportation during
    requirements for, 2298
Anesthesia machine(s), 2291, *2292*
Anesthetic agent(s), 2293-2295. *See also* particular drugs
  effects on electrocardiogram, 751
  factors in choice of, 2293
  hemodynamic effects of, 2294t
  intravenous
    kinetics of, 2294-2295
  local
    effect on delayed afterdepolarizations, 315
  minimum alveolar concentration (MAC) of, 2294
  scavenging from operating room environment, 2291
  uptake and distribution of, from lungs, 2294
Anesthetic breathing system(s), 2291, *2292-2293*
Aneuploidy, 176
Aneurysm(s)
  after cardiac trauma, 2536, 2538
  aortic. *See* Aortic aneurysm(s)
  cerebral
    coarctation of the aorta and, 1366-1367, 2031-2032, 2311
    mycotic, rupture of, 2309
  coronary artery
    in Kawasaki disease, 1546, *1547-1549*, 1552-1554, *1553-1554*, *1558*
  false
    after myocardial infarction, 2283
  of ductus arteriosus, 1063
    after surgical ligation, 2027
  peripheral
    causes of, 993
    in Kawasaki disease, 1546, 1552
    Salmonella infection of, 2469
  vein of Galen, 1474
  ventricular
    after myocardial infarction, 1716, 2283
    click associated with, 687
    left ventricular outflow obstruction due to, 1195
    ventricular septal defect with, 1005
Aneurysm clip(s)
  intracranial
    nuclear magnetic resonance and, 873
Aneurysmal bone cyst
  embolization for, 992
Aneurysmal dilatation of right ventricular outflow tract patch
  after tetralogy of Fallot repair, *2037*, 2037
Anger camera. *See* Gamma camera(s)
Angina, 2282
  Heberden's description of, 2277
  Prinzmetal's (vasospastic), 1713, 2283-2284
Angiocardiography, 952-962. *See also* Angiography
  axial, 954-955, *955-956*
  cine
    ventricular volume calculations from, 497
  contrast agents for, 952t-953t, 952-954
  cranial angulation in, 961
  radionuclide. *See* Blood pool imaging; Nuclear cardiology

Angiocardiography *(cont.)*
x-ray projections for, 954-961, 955t, *955-956*
aortic orifice, 961
for congenital heart defects, 957t-960t
four-chamber, 961, 1265
hepatoclavicular, 961
lateral, 955
left anterior oblique, 955-960
long axial, 960-961
posteroanterior, 955
right anterior oblique, 955-960
right ventricular outflow tract, 961
sitting-up, 961
tilted left anterior oblique, 960-961
Angiodynography. *See* Doppler echocardiography, color
Angiography. *See also* Angiocardiography
aortic occlusion, 962
coronary, 968-972
anticoagulation for, 969
development of, 2279
indications for, 968-969, 969t
problems and complications of, 970
technique for, 969-970
digital subtraction. *See* Digital subtraction angiography
nuclear magnetic resonance, 869-871, 994
peripheral vascular, 973-996
contraindications to, 974
contrast agents for, 974, 975t, 975, 994
minipuncture technique for, 994
of abdominal aorta, 980-984
of pelvis and extremities, 988-993
of thoracic aorta, 975-980
risks of, 974-975
pulmonary artery wedge, 961
pulmonary venous wedge, 961-962
radionuclide. *See* Blood pool imaging; Nuclear cardiology
renal, 984-988
Angioma
capillary, 1472-1473, *1474-1475*
cardiac, 1652
syndromes associated with, 1471t
Angioplasty
percutaneous transluminal. *See* Balloon angioplasty
Angiotensin I, 464. *See also* Renin-angiotensin-aldosterone system
conversion of
in lungs, 365
effects on pulmonary circulation, 374t, 376
Angiotensin II, 464. *See also* Renin-angiotensin-aldosterone system
effects on pulmonary circulation, 374t, 376
in endothelial prostacyclin release, 366
renal handling of sodium and, 458
synthesis of
in lungs, 365
Angiotensin inhibitor(s)
effects on pulmonary circulation, 374t, 378
Angiotensin-converting enzyme (ACE), 365
Angiotensin-converting enzyme inhibitor(s). *See also* particular drugs
effects on pulmonary circulation, 374t, 378
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2367
Angular frequency
defined, 616
Angular momentum
defined, 616
Angulation error
in positron emission tomography, 620
Ankylosing spondylitis, 1536
cardiovascular manifestations of, 1537
Annihilation photon(s)
defined, 623
Annulus(-i) fibrosus(-i), 111
of mitral valve, 117-118
of tricuspid valve, 114
Anomalous coronary artery(-ies), 970-972, *971-972*, 1453-1461
chest pain due to, 1949
coronary artery disease with, 2281
echocardiographic assessment of, 775-776
left
complicating tetralogy of Fallot repair, 2213
congestive heart failure due to, 2013
electrocardiographic findings in, 745-746, *748*, *1704*, 1706, 1707t, *1708*
endocardial fibroelastosis vs., 1626
from pulmonary artery, 971-972, *971-972*, 1454-1457, *1455-1457*
from right sinus of Valsalva, 1457-1458, *1458*
management of, 1967
myocardial infarction due to, 745-746, *748*, 1685
myocardial perfusion scintigraphy in assessment of, 845
myocarditis vs., 1585
radiographic findings in, 703
surgical reperfusion for, 1718-1719
myocardial infarction due to, 745-746, *748*, 1685, 1714
nuclear magnetic resonance imaging of, 863
right
from left sinus of Valsalva, 1458
from pulmonary artery, 1457
single, 1458
myocardial infarction due to, 1714
with double-outlet right ventricle, 971, 1223-1226, *1227*, 1460
with tetralogy of Fallot, 970-971, 971t, 1077
complicating repair, 1096, 2213
with truncus arteriosus, 1128-1129
Anomalous pulmonary venous connection(s), 1145-1167. *See also* Scimitar syndrome
embryology of, *1146-1147*, 1146-1147
history of, 1145-1146
management of
with sinus venosus atrial septal defect repair, 2029
partial, 1147-1153
cardiac catheterization and angiographic findings in, 1151-1152, *1152*
clinical features of, 1150-1152
defined, 1145
echocardiographic features of, 1150-1151
electrocardiographic features of, 1150
embryology of, *1147*, 1147
management of, 1152-1153, *1153*
natural history of, 1152
nuclear magnetic resonance imaging in, 862, 1152
physiology and hemodynamics of, 1149-1150
radiographic features of, 697, 1150
radionuclide studies in, 1152
types of, *1148*, 1148-1149
with atrioventricular canal defect, 1045
surgery for, 2215
clinical caveats for, 2299t
total. *See* Total anomalous pulmonary venous connection
Anorexia nervosa, 1670
ipecac abuse in, 1673
Anorexigen(s)
effects on pulmonary circulation, 379
Anoxia
defined, 266, 1686
Anoxic spell(s). *See* Tetralogy spell(s)
Antacid(s)
digoxin interaction with, 2363
magnesium-containing
hypermagnesemia due to, 2435
mexiletine absorption and, 2367
Anterior fascicular block. *See* Left anterior hemiblock
Anthracycline(s). *See also* Doxorubicin
cardiotoxicity of, 1672-1673, 2338-2341, 2341t
Antiarrhythmic agent(s), 2126-2134, 2550t-2552t. *See also* particular drugs
absorption of
in neonate, 471
aggravation of conduction system disease by, 1797
cimetidine interaction with, 2367
class IA, 2128-2129, 2550t
in atrial flutter treatment, 1856
in ventricular arrhythmia management, 1898
pharmacology of, in hepatic, gastrointestinal or nutritional disorders, 2365
class IB, 2129-2130, 2550t
in ventricular arrhythmia management, 1898-1899
pharmacology of, in hepatic, gastrointestinal or nutritional disorders, 2365
class IC, 2130-2131, 2550t-2551t
in atrial flutter treatment, 1856
in ventricular arrhythmia management, 1899
pharmacology of, in hepatic, gastrointestinal or nutritional disorders, 2365-2366
class II. *See* Beta blocker(s)
class III, 2132, 2551t
in atrial flutter treatment, 1857
in ventricular arrhythmia management, 1899
pharmacology of, in hepatic, gastrointestinal or nutritional disorders, 2366
class IV. *See* Calcium channel blocker(s)
classification of, 1856-1857, 2127t
dosage adjustment for renal insufficiency, 471, 2441t
effects on electrocardiogram, 749-751
hepatic metabolism of, 470
in atrial flutter treatment, 1856-1857
in ventricular arrhythmia management, 1898-1899
metabolites of
clinical importance of, 473
plasma-level monitoring of, 472-473
prediction of efficacy of
with electrophysiology studies, 1880
with transesophageal pacing, 2165
protein-binding of
developmental considerations in, 470
interactions involving, 474
plasma-level monitoring and, 472-473
renal excretion of
interactions involving, 474
sinus node dysfunction due to, 1775
management of, 1778
syncope due to, 1941
use of, in pregnancy, 2385-2386, 2386t
Antibiotic(s), 2047-2064. *See also* particular drugs and classes of drugs
administration of

in cardiac catheterization, 963
anthracycline. *See also* Doxorubicin
cardiotoxicity of, 1672-1673, 2338-2341, 2341t
beta-lactam, 2051-2056
mechanism of action of, 2051
structure of, *2051*
choice of, 2047-2049
for infective endocarditis, 1571-1573, 1572t
parenteral
recommended doses for children with severe infections, 2057t
prophylactic. *See* Antibiotic prophylaxis
tests for microbial sensitivity to, 1571, 2048
Antibiotic prophylaxis, 2050-2051
for asplenic children, 1293, 2473
for endocarditis, 1566-1568, 1567t-1568t, 2050-2051
during pregnancy, 2384, 2387-2388
with mitral valve prolapse, 1981-1982, 1983
in rheumatic fever management, 1498-1499, 2050
in rheumatic heart disease management, 1520, 2050
postoperative, 2261
Anticancer agent(s). *See* Chemotherapy; particular drugs and classes of drugs
Anticoagulant(s), 2079-2081, 2553t. *See also* particular drugs
antimicrobial interactions with, 2052
effects on pulmonary circulation, 379
for venous thrombosis, 2083
in cardiopulmonary bypass, 2300
in cor pulmonale management, 2505
in coronary artery disease management, 2285
in idiopathic dilated cardiomyopathy management, 1624
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2367
surgery during chronic therapy with, 2080-2081
use during pregnancy, 2080, 2381-2382
Anticodon(s), 6
defined, 60
Anticonvulsant(s). *See also* particular drugs
antibiotic interactions with, 2049
systemic lupus erythematosus and, 1532, 1533
Antidepressant(s). *See* Tricyclic antidepressant(s)
Antidiuretic hormone (ADH; vasopressin)
changes in, in space, 437-438
effects on pulmonary circulation, 374t, 377
hydroosmotic response to, in collecting ducts, *455*, 455
in fetal cardiovascular response to stress, 287
in gastrointestinal hemorrhage management, 984
in regulation of extracellular fluid osmolality, 459
regulation of, 2495
after heart transplantation, 2495
Antiferromagnetic substance(s), 603
Antifungal agent(s), 2061. *See also* particular drugs
Antihypertensive agent(s), 2434t. *See also* particular drugs and classes of drugs
dosage adjustment for renal insufficiency, 2440t
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2366-2367
use of, during pregnancy, 2386-2387, 2387t
Anti-inflammatory agent(s). *See also* Steroid(s); particular drugs
in rheumatic fever management, 1499
nonsteroidal
antiplatelet effects of, 2081
for myocardial protection, 270
Anti-interleukin-2 receptor antibody
in rejection management, 2249
Antilirium (physostigmine)
in obstetric management, 2389
Antilymphocyte globulin (ALG)
in heart transplantation management, 2235, 2244
Antimicrobial therapy, 2047-2064. *See also* particular drugs and classes of drugs
dose, route and duration of, 2051
empiric, 2050
failure to respond to, 2061
host factors in, 2048-2049
principles of, 2050-2051
prophylactic, 2050-2051. *See also* Antibiotic prophylaxis
single- vs. multiple-drug, 2050
superinfection and resistance during, 2051
synergism in, 2050
Antimycobacterial agent(s), 2060. *See also* particular drugs
Antinuclear antibody(-ies)
in systemic lupus erythematosus, 1530
drug-induced, 1533
Antiparallel
defined, 60
Antiplatelet agent(s), 2081-2082, 2553t. *See also* particular drugs
in coronary artery disease management, 488, 2285
in pulmonary vascular disease management, 2003
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2367
Antiscatter grid (bucky grid), 555, 638
Antisense
defined, 60
Antistreptolysin O antibody
in rheumatic fever diagnosis, 1495
Anti-Tac antibody
in rejection management, 2249
Antithymocyte globulin (ATG)
in heart transplantation management, 2235, 2244
Antiviral agent(s), 2061
Aorta. *See also* Aortic arch(es)
anatomy of, 120-121
circumflex, 1431
Doppler assessment of flow in, 793, 794-795, *794-797*
in fetus, 822
dorsal, 93
ductus arteriosus vs.
in fetal echocardiography, 810
echocardiographic assessment of, *776*, 776-777, *780*
isthmus of, 120, 1354
measurement of cross-sectional area of, 794, *796*
morphologic changes in, after birth, 132
nomenclature for segments of, 1354, *1355*
normal growth of, 1369
right circumflex, 1426
rupture of
coarctation of the aorta and, 1367
size of
in fetus, 819
trauma to, 2537
computed tomography in assessment of, 883-897, *894*
thoracic aortography in management of, 978, *980*
tubular hypoplasia of, 1354
defined, 1357
velocity of blood flow in, 793
Doppler measurement of, 794, *797*
Aortic aneurysm(s), 978-980, *980*
after balloon angioplasty for coarctation, 1371, 2197, *2198*
after coarctation repair, 1372-1373, 2033, *2034*
after surgery for aortic valve stenosis, 2034
computed tomography assessment of, 883
dissecting
coarctation of the aorta and, 1367
false
after cardiac trauma, 2537
mycotic, 978-980, *980*
Salmonella infection of, 2469
Aortic arch(es)
anomalies of, 1421-1452
anatomy of, 1425-1429
cardiac catheterization and angiography in, 1438-1439
classification of, 1424
course, treatment and prognosis with, 1439-1444
diagnostic evaluation of, 1431-1439, *1432-1438*
echocardiographic examination in, 1433-1438, *1436-1438*
embryology of, 1421-1423, *1422-1423*
etiology of, 1424
radiologic examination of, 1431-1433, *1432-1435*
symptoms and signs of, 1431
cervical
anatomy of, *1428*, 1428-1429
course, treatment and prognosis in, 1443, *1444*
embryology of, 1423, 1428-1429
signs and symptoms of, 1431, 1443
double
anatomy of, *1425*, 1425-1426
course, treatment and prognosis in, 1440-1441, *1442*
echocardiographic identification of, 1434, *1438*
embryology of, 1422-1423
pulmonary findings with, 2509
radiologic examination in, 707, 1431-1433, *1432*
with segmental atresia of one arch, *1425*, 1425-1426, 1440, 1441
embryonic, 90-96, *94-97*
interrupted, 1373-1379
abnormalities associated with, 1374
anatomy of, 1373-1374, *1374-1375*
cardiac catheterization and angiography in, 1377-1378
clinical features of, 1376-1377, *1377*
defined, 1373
digital subtraction angiography in, *910*
embryology of, 1374-1376, *1376*
followup and outcome in, 1378-1379
medical management of, 1378, 2119-2120
natural history of, 1378
physiology of, 1376
surgery for, *1375*, 1378, 1962, 2216-2217, *2218*

Aortic arch(es) *(cont.)*
left, with anomalous branching, *1427,* 1427-1428
course, treatment and prognosis in, 1439-1440, *1440*
normal left
anatomy of, 1424-1425
relative segment diameters of, 1354
right
anatomy of, *1426-1427,* 1426-1427
computed tomography assessment of, 883, *890*
congenital heart disease with, 1427
echocardiographic assessment of, *776,* 776, 1434, *1436*
embryology of, 1423
position of ductus arteriosus with, 1055, 1426, *1426-1427*
pulmonary findings with, 2509
radiographic findings in, 707
with anomalous left subclavian artery, 1426, 1427, *1427,* 1441-1443, *1443*
with mirror-image branching, *1426,* 1426, 1427
with tetralogy of Fallot, 1082
Aortic arch body(-ies)
in control of breathing, 358
Aortic atresia
echocardiographic assessment of
in fetus, 811
in hypoplastic left heart syndrome, 1316-1317
Aortic blood acceleration
as contractility index, 226
Aortic bulb. *See* Aortic sac
Aortic cross-clamping
myocardial protection during, 272-273
spinal cord injury due to, 1371, 2259, 2313, 2455
Aortic cusp
noncoronary, 1453
Aortic diastolic pressure
decreased
coronary vascular reserve in, *262,* 262
in cardiopulmonary resuscitation, 412
Aortic dissection
coarctation of the aorta and, 1367
computed tomography assessment of, 883, *893*
nuclear magnetic resonance imaging in, 856, *858*
Aortic insufficiency
after surgery for aortic stenosis, 1343, 2034
after ventricular septal defect repair, 2031
computed tomography assessment of, 903
Doppler assessment of, 791, *793*
in juvenile rheumatoid arthritis, 1529
in spondyloarthropathies, 1537
in systemic lupus erythematosus, 1532
in tetralogy of Fallot, 1077
murmur of
changes in, in pregnancy, 2377
rheumatic mitral stenosis vs., 1511
radionuclide angiographic evaluation of, 842
rheumatic, 1512-1518
auscultatory findings in, 1515-1516
cardiac catheterization and angiography in, 1517
clinical manifestations of, 1515-1517, *1516-1517*
course and prognosis in, 1517
diagnosis of, 1518
differential diagnosis of, 1518
echocardiographic findings in, 1516-1517, *1517*
electrocardiographic findings in, *1516,* 1516
in pregnancy, 2378
pathology of, 1512, *1514*
pathophysiology of, 1512-1515, *1514*
prognostic indicators in, 1516-1517
timing of surgery in, 1522
unoperated
ventricular arrhythmias with, 1891
vasodilators for, 2093
ventricular septal defect with, 1005
patent ductus arteriosus vs., 1065
Aortic isthmus, 120, 1354
Aortic knob, 120
Aortic occlusion angiography, 962
Aortic override
in tetralogy of Fallot, 1076-1077
Aortic pulmonary window
patent ductus arteriosus vs., 1064
Aortic sac, 81, 91-93
Aortic sinus. *See* Sinus(es) of Valsalva
Aortic stenosis, 1334-1352
angiographic views for, 957t
balloon dilation for, 1343, 2190-2192, *2193-2194*
calcific
coarctation of the aorta and, 1373
chest pain due to, 1949
congenital
recurrence risk for, 176t
critical, 1962
defined, 1341
prostaglandin therapy in management of, 2120
echocardiographic assessment of
in fetus, 811, *814*
in hypoplastic left heart syndrome, 1317
murmur of
changes in, in pregnancy, 2376
innocent pulmonary murmur vs., 1923
Still's murmur vs., 1923
supraclavicular bruit vs., 1924
myocardial infarction in, 1706-1707
obstetric anesthesia with, 2390
pregnancy with, 2379
presenting at age 4-12 months
management of, 1968
radiographic findings in, 703, *707*
rheumatic, 1512
auscultatory findings in, 1515
pathology of, 1512
pathophysiology of, 1514-1515
pulse in, 1515
symptoms of, 1515
subvalvular, 1346-1349
anatomy and embryology of, 1346
cardiac catheterization in, 1347, *1348*
clinical features of, 1346
echocardiographic findings in, 1346-1347, *1347*
in double-outlet right ventricle, 1217-1218, 1223
in single ventricle, 1271, *1272*
lesions associated with, 1346
natural history of, 1347-1348
physiology of, 1346
treatment and followup in, 1348-1349
ventricular septal defect with, 1005
supravalvular, 1343-1346
anatomy and embryology of, 1343-1344
cardiac catheterization and angiography in, 1344-1345, *1345*
clinical features of, 1344
molecular basis of, 55
myocardial infarction and, 1712-1713
natural history of, 1345
noninvasive evaluations in, 1344, *1345*
physiology of, 1344
treatment of, 1345-1346
surgical decisions and techniques for, *2219-2221,* 2222
syncope in, 1930-1931
unoperated
ventricular arrhythmias with, 1891
valve area calculation in
from cardiac catheterization data, 941t-943t, *941-943,* 941-944, *1340,* 1341
from Doppler findings, 799
valvular, 1334-1343
anatomy and embryology of, *1335,* 1335
cardiac catheterization in, *1340-1341,* 1340-1341
clinical features of, 1336-1337
Doppler vs. cardiac catheterization pressure gradients in, 1338-1339, *1339-1340*
echocardiographic findings in, 1338-1340, *1339-1340*
electrocardiographic findings in, 1337-1338
etiology of, 1335-1336
exercise test in, 1338
in double-outlet right ventricle, 1223
left ventricular changes in, 1335
malformations associated with, 1334
natural history of, 1334-1335
participation in competitive sports after surgery for, 2034
physiology of, 1336
pulmonary valve stenosis vs., 1396
roentgenographic findings in, 1338
sudden death in, 1336, 1342
surgical treatment of, 2033-2035
treatment and followup in, 1341-1343
Aortic thrombosis
in neonate, 2488-2489
Aortic valve
anatomy of, 119-120
area of. *See* Aortic valve area
balloon dilation of, 1343, 2190-2192, *2193-2194*
bicuspid, 1334, *1335,* 1335
echocardiographic appearance of, 1338, *1339,* 1360-1361
with coarctation of the aorta, 1354-1356, 2031
blood flow across
calculation of, 942t, 943
Doppler assessment of, 791-793, *793*
Doppler quantitation of, 794-795
velocity of, in fetus, 821
calcification of
after surgery for aortic stenosis, 2034
echocardiographic assessment of, 774, *775*
replacement of
in aortic valvular stenosis, 1343
ventricular arrhythmias after, 1896
trauma to, 2536
unicuspid, *1335,* 1335
Aortic valve area
calculation of, *941-943,* 941-944, *1340,* 1341
by Bache formula, *943,* 943t, 944
by Gorlin formula, 941t
errors in, 944
importance of accurate cardiac output measurement in, 943t, 944
Doppler estimation of, 799

Aortic valve disease. *See* Aortic insufficiency; Aortic stenosis
Aortic valvotomy
  balloon, 1343, 2190-2192, *2193-2194*
  complications of, 2034
  for aortic valvular stenosis, 1342-1343
    results of, 1341-1342, 1342-1343
  patient selection for, 2034-2035
  residua of, 2034
  sequelae of, 2034
  ventricular arrhythmias after, 1896
Aortic valvulitis
  in rheumatic fever, 1493
Aortic vestibule, 119
Aortitis
  salmonella, 2469
Aortography
  abdominal, 980-984
  occlusion, 962
  thoracic, 975-980
Aortoplasty
  patch graft
    for coarctation of the aorta, 1368
Aortopulmonary collateral artery(-ies)
  in tetralogy of Fallot, 1074-1075, *1075*
    development of, 1078
    management of, at surgical repair, 1094
    postoperative problems due to, 1096
Aortopulmonary septum, 88-89, *92*
Apex beat, 683
Apex impulse, 683
Apnea
  reflex, 1431
Apneic facial immersion. *See* Diving reflex
Apneustic center, 357
Apolipoprotein(s), 42, 43t, 476-477, 477t. *See also* particular apolipoproteins
  genes for, 45-46, *46-47*
Apolipoprotein A-I (apoA-I), 43t, 46, *47*, 476
  plasma levels of
    atherosclerosis and, 481
Apolipoprotein A-IV (apoA-IV), 43t, 45
Apolipoprotein B (apoB), 42, 43t, 45-46, *46*, 476
  plasma levels of
    atherosclerosis and, 480-481
Apolipoprotein C (apoC), 45
Apolipoprotein C-III (apoC-III), 43t, 46, *47*
Apolipoprotein E (apoE), 46
  genetic variant of
    in Type III hyperlipidemia, 45, 478
Appendicitis
  electrocardiographic findings in, 754
Appetite suppressant(s)
  effects on pulmonary circulation, 379
Apresoline. *See* Hydralazine
Ara-A (adenine arabinoside), 2061
Arachidonic acid, 477
  mono-oxygenase metabolite of
    in regulation of ductus arteriosus closure, 2112
  products of. *See also* Leukotriene(s); Prostaglandin(s)
    in pathogenesis of pulmonary hypertension, 373
Arachnocytosis of the heart muscle. *See* Ventricular tachycardia, incessant, in infants
Arachnodactyly
  congenital contractural, 2397
  congenital heart disease with, 678t, 679
Archipelagos, 125
Arginine vasopressin. *See* Antidiuretic hormone
Arrhythmia(s), 1723-1916. *See also* Ventricular arrhythmia(s); particular arrhythmias
  after direct-current countershock, 2169t, 2169-2170
  chest pain due to, 1949
  clinical applications of body surface mapping in, 519-520, *520*
  complicating cardiac catheterization, 966
  diagnosis of
    ambulatory electrocardiography in, 1728-1735, *1730-1737*, 1731t-1733t
    esophageal electrocardiography in, 1727-1728, *1728-1729*, 2162-2163, *2163*
    event recording in, 1735-1737
    exercise electrocardiography in, 1737-1740, *1738-1741*
    history and physical examination in, 1726-1727
    noninvasive, 1725-1742
    signal-averaged electrocardiography in, 1740-1741, 2164
    standard electrocardiography in, 1727-1728, *1727-1729*
    techniques for recording atrial activity in, 2162-2164, *2163*
  due to beta-adrenergic bronchodilators, 2506
  due to cardiac trauma, 2535
  due to theophylline, 2506
  electrical treatment of, 2162-2173
  fetal, 1905-1911
    diagnosis of, 812-818, *814-819*, *1906-1907*, 1906-1907
    hydrops fetalis and, 1905-1906, *1907*
    incidence of, 812
    parents' reaction to management of, 2520
  in pregnancy, 2381-2382
  in rheumatic heart disease, 1520
  innocent, 1951-1958
    evaluation of, 1951
  intraoperative, 2298
  mechanisms of, 311-317
  neurologic symptoms due to, 2322-2323
  postoperative, 2257-2258
    after atrial septal defect repair, 1035, 1036, 2029
    after intra-atrial baffle procedure, 1195, 1205, 2041, 2263
    after Rastelli operation for transposition of the great arteries, 1209
    after tetralogy of Fallot repair, 1081, 1097
  reentrant. *See also* Reentry
    mechanisms of, 311-312, *312*
  reperfusion, 269
  sinus. *See* Sinus arrhythmia
  sudden death and, 675
  surgical treatment for, 2174-2182
  syncope secondary to, 1932-1937, *1933-1940*, 1936t
    in normal heart, 1932
  triggered
    mechanisms of, 314-316
  vagal, 1952-1955, *1953*
    symptomatic, 1953-1954
  with atrial septal defect, 1027
    postoperative, 1035, 1036, 2029
  with Ebstein's anomaly, 1137
  with mitral valve prolapse, 336-337, 1982
    management of, 1983
  with myocardial infarction, 1715-1716
    management of, 1718
  with partial anomalous pulmonary venous connection, 1150, 1152
Arrhythmogenic right ventricular dysplasia, 1636-1640, 1893-1894
  clinical findings in, 1637, 1893
  diagnosis of, 1876
  differential diagnosis of, 1637
  etiology of, 1637
  laboratory investigations in, 1638-1639, *1638-1640*
  natural history of, 1639-1640
  pathology of, 1636-1637, 1893
  prevalence of, 1637, 1893
  syncope in, 1932
  treatment of, 1639, 1894, 2181
Arterial arch(es), 91, *94*
Arterial baroreceptor reflex(es). *See* Baroreflex(es)
Arterial blood oxygen content, 290
  in newborn, 291
Arterial cannulation
  for cardiopulmonary bypass, 2301
  for intraoperative monitoring, 2295
Arterial hepatic dysplasia. *See* Alagille syndrome
Arterial impedance, 224, 235-236
Arterial ring, 104
Arterial supraclavicular bruit, 1922t, *1923*, 1923-1924
Arterial switch procedure, 1206-1207, *1207*, 2039, 2213-2214, *2215*
  angiographic views for postoperative assessment of, 959t
  coronary artery disease after, 1686, 2041
  great vessel obstruction after, 2041
Arterial thrombosis. *See* Thrombosis
Arterial valve(s). *See* Semilunar valve(s)
Arterial venous oxygen difference
  defined, 927
Arteriography. *See* Angiography
Arteriohepatic dysplasia. *See* Alagille syndrome
Arteriole(s), 121
Arteriopulmonary fistula
  patent ductus arteriosus vs., 1065, *1066*
Arteriosclerosis. *See* Atherosclerosis; Coronary artery disease
Arteriovenous fistula(e), 1471-1481
  classification of, *1472*, 1472t, 1472-1474
  congenital
    congestive heart failure due to, 2012
  distribution of, 1473t
  embryology of, 1471-1472, *1472*, 1472t
  history of, 1471
  macrofistulous, 1473-1474, *1476-1478*
  murmur of
    mammary souffle vs., 1926
    venous hum vs., 1926
  patent ductus arteriosus vs., 1065
  presenting in first 2 weeks of life
    management of, 1965
  pulmonary
    echocardiographic assessment of, 777
    patent ductus arteriosus vs., 1066
  synonyms for, 1471t
  systemic
    echocardiographic assessment of, 777
  treatment of, 1474-1479
  truncal, 1474, *1477-1478*
Arteritis
  coronary. *See* Coronary arteritis
  salmonella, 2469
  Takayasu's. *See* Takayasu's arteritis
Artery(-ies). *See also* particular arteries
  anatomy of, 120-121, *122*
  balloon dilation of. *See* Balloon angioplasty
  cell biology of
    atherosclerosis and, 483-487

Artery(ies) *(cont.)*
classification of, 121
diffuse intimal thickening in, 484
elastic, 121, *122*
embryology of wall of, 483-484
growth response of
to flow, 484
muscular, 121, *122*
response of, to wall tension, 484
smooth muscle cells of, 484-485
in atherosclerosis, *484*, 484-485
Arthritis
bacterial
rheumatic fever vs., 1497
fever with
differential diagnosis of, 1497
in inflammatory bowel disease, 1536
in rheumatic fever, 1491, 1492
in systemic lupus erythematosus, 1530
reactive, 1536
rheumatoid. *See* Rheumatoid arthritis
Arthrochalasis multiplex congenita, 2404t
Arylsulfatase B deficiency
in Maroteaux-Lamy syndrome, 1660
Aschoff's nodule, *1490*, 1490
Ashman phenomenon, 1795-1796
Aspartylglycosaminuria, 1662
Aspergillus
infective endocarditis due to, 1570
intracranial infection due to, after heart transplantation, 2245
Asphyxia
cardiopulmonary resuscitation for
epinephrine in, 410-412
sodium bicarbonate in, 416-417
neonatal
complications of, 2479-2480
resuscitation and stabilization for, 2478-2480
perinatal
myocardial infarction and, 1707
pulmonary edema due to, *395*, 395-396
Aspirin (acetylsalicylic acid), 2553t
antiplatelet therapy with, 2081
dosage adjustment for renal insufficiency, 2440t
in Kawasaki disease management, 1556, 1557
in pulmonary vascular disease management, 2003
in rheumatic fever management, 1499
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2367
Asplenia
congenital. *See* Asplenia syndrome
functional
in sickle cell disease, 2473
Asplenia syndrome (right isomerism), 695, 1289-1295, 1297-1298, 2405-2406
antibiotic prophylaxis in, 1293, 2473
atrioventricular canal defects with, 1045
cardiovascular abnormalities associated with, 1293t, 1293
clinical features of, *1289-1293*, 1289-1293
defined, 1288
echocardiographic assessment of, 769, *770*
in fetus, 807
electrocardiographic findings in, 724, 1289
immunization recommendations for, 1293, 2473
immunologic status in, 1293
incidence, etiology and genetics of, 1288-1289
management and prognosis in, 1293-1295
renal abnormalities in, 2430t
total anomalous pulmonary venous connection with, *1156*, 1156
Asthma
chest pain due to, 1948
Asymmetry
in embryo, 158-159
in heart tube
cardiac looping and, 157-158, 158t
Asystole
cardiopulmonary resuscitation for
calcium in, 411, 418
Atenolol, 2132, 2551t
for ventricular arrhythmias, 1899
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2365
use of, in pregnancy, 2386t
Atherosclerosis. *See also* Coronary artery disease
after cardiac transplantation, 1993, 2237, 2280
cell biology of arteries and, 483-487
diabetes and, 1992, 2495-2496
inflammatory response and, 487
lesion development in, *487*, 487-488
lipid metabolism and, 475-491
myocardial infarction in, 1712
myocardial perfusion scintigraphy in assessment of, 845
nuclear magnetic resonance imaging in, 864, 866
pathologic hallmarks of, 475
prevalence of
in children, 1987
prevention of, 488-489, 1987-1993
risk factors for, 475, 488-489, 1713t, 1989-1993
contraceptive choice and, 2372
smooth muscle proliferation in
altered gene expression and, 485
cholesterol deposits and, 488
macrophages and, 486-487
platelet-derived growth factor and, 485
thrombosis and, 488
Athletics
classification of, 2273, 2273t
participation in
after cardiac rehabilitation, 2272-2273, 2273t
after surgery for aortic valve stenosis, 2034
for pacemaker patients, 2148, 2149
importance of, in normal childhood, 2267
with pulmonary stenosis, 1405-1406
Atlanto-axial instability
in Down syndrome, 2456
Atom(s)
partially stable, 560
stable, 559-560
structure of, 559
unstable, 560
Atomic number, 559
Atomic weight, 559
Atracurium, 2295t
Atresia of the common pulmonary vein. *See* Pulmonary vein atresia, common
Atrial appendage(s)
juxtaposed
with tricuspid atresia, 1119
left, 117
right, 112
Atrial baffle procedure(s). *See also* Mustard operation; Senning operation
for transposition of the great arteries, 1203-1206, *1204*
protein-losing enteropathy after, 2260
for ventricular inversion with normally connected great arteries, 1244
in pulmonary vascular disease management, 2003-2004
Atrial bigeminy, *1956*
blocked, 1956
fetal, 1907
Atrial cardiocyte(s), 2496
Atrial contraction
ventricular preload and, 233
Atrial extra stimulus technique
for sinoatrial conduction time assessment, 1768-1770, *1769-1770*
Atrial extrasystole(s). *See* Premature atrial contraction(s)
Atrial fibrillation, 1858-1861
clinical manifestations of, 1860-1861
in pregnancy, 2381-2382
mechanisms of, 1858-1860
syncope in, 1934
treatment of, 1861, 2171
with aberrant ventricular conduction
premature ventricular contractions vs., 1865-1867, *1870*
Atrial flutter, 1759, *1761-1762*, 1849-1858
age at onset of, 1853
anatomy and hemodynamics of, 1853
characteristics of, 2546t
congenital heart defects and, 1852-1853
defined, 1849, *1849-1850*
electrophysiology study in, 1854
esophageal electrocardiography in diagnosis of, 1854, 2162-2163
exercise electrocardiography in assessment of, 1740, *1741*
fetal, 817, 1851-1852, 1908, *1909-1910*, 1910t
echocardiographic diagnosis of, 814, 815, *819*
in newborn and infant, 1851-1852
in older child and adolescent, 1852-1853
in pregnancy, 2381-2382
inapparent, 1854, *1855-1856*
long-term followup in, 1854-1855
mechanisms of, 1849-1851
postoperative, 2258
presentation of, 1853-1854
rapid atrioventricular conduction with, 1853-1854, *1854*
reentry in, 1849-1850
supraventricular tachycardia vs., *1820*, 1820
syncope in, 1934
transesophageal pacing for, 1858, 2167
treatment of, 1855-1858, *1857*, *1859-1860*, 2171
emergency, 2546t
with aberrant ventricular conduction
premature ventricular contractions vs., 1865-1867, *1870*
Atrial isomerism
left. *See* Polysplenia syndrome
right. *See* Asplenia syndrome
Atrial natriuretic factor (ANF), 458-459, *459*, 2496
production of
cardiac conductive-tissue pathways and, 167
role of, in congestive heart failure, 245, 2426-2427
molecular basis of, 56-57
ventricular secretion of, 56
Atrial premature contraction(s). *See* Premature atrial contraction(s)
Atrial pressure

left. *See* Left atrial pressure
right, 918
Atrial septal defect, 1023-1036
anatomic features of, 1025-1026
angiographic assessment of, 957t, 1033, *1034*
atrial flutter and, 1852-1853
auscultatory findings in, 1029-1030
cardiac catheterization in, 1033
cardiovascular defects associated with, 1026
physiology in, 1027
coronary sinus, 1026
development of, 1025
prognosis after repair of, 1036
repair of, 1034-1035
definitions and classification of, *1024*, 1024
echocardiographic assessment of, 773, *773-774*, 1031-1033, *1032*
electrocardiographic findings in, 1030, *1031*
embryology of, 1024-1025
epidemiology of, 1025
familial
with prolonged atrioventricular conduction, 1025
fixed splitting of second heart sound in, 686, 1029
genetic aspects of, 1025
in atrioventricular canal defect
echocardiographic examination of, 1044
incomplete right bundle branch block in, 734
management of, 1033-1035, 1968
murmur of, 1029-1030
innocent pulmonary murmur vs., 1923
Still's murmur vs., 1923
natural history of, 1027-1028
nuclear magnetic resonance imaging of, *859*, 859, 1033
occlusion device for, 2206-2208
ostium primum
complications of repair of, 2029
in atrioventricular canal defects, 1037-1038
isolated, 1039
physical examination in, 1028-1030
physiology of, 1026-1027
posterior and inferior to fossa ovalis, 1026
pregnancy and, 1028, 2378-2379
prognosis in, 1035-1036
pulmonary valve stenosis vs., 1396
radiographic findings in, 697, *698*, 1030, *1031*
radionuclide angiocardiographic studies of, 1033
recurrence risk for, 176t
repair of
complications, residua and sequelae of, 2029
electrophysiology of arrhythmias after, 2159
fragmentation hemolysis after, 2345
patient selection for, 2029
secundum, 1025-1026
acquired cardiovascular pathology associated with, 1026
body surface map findings in, 519
development of, 1025
electrocardiographic findings in, 1030, *1031*
repair of, 1033-1034, 2028
sinus node dysfunction after repair of, 1776
sinus venosus, 1026
arrhythmias after repair of, 1036, 1776
complications of repair of, 2029
development of, 1025
electrocardiographic findings in, 1030
partial anomalous pulmonary venous connection and, 1151, 2029
repair of, 1034
spontaneous closure of, 1028
traumatic, 2537
with mitral stenosis. *See* Lutembacher's syndrome
with partial anomalous pulmonary venous connection, 1149-1150
with pulmonary valve stenosis, 2035
with tricuspid atresia, 1119
Atrial septectomy. *See* Blalock-Hanlon operation
Atrial septostomy, 2183-2188
balloon, 1195-1197, *1196*, *1199*, 2184-2185, *2185*
after blade septostomy, *2187-2188*, 2187-2188
indications for, 1964
procedure for, 1196-1197, *1199*, 2184
with echocardiographic guidance, *1189*, 1190, 1197
blade, 1197-1199, *1199-1200*, 2185-2187, *2186-2188*
in adult patient, 2188
procedure and technique for, 1197-1199, 2185-2187
echocardiographic assessment of results of, 773, *774*
for primary pulmonary hypertension, 2003
for total anomalous pulmonary venous connection, *1162*, 1162, 1163
for transposition of the great arteries
indications for, 1190
results of, 1202
for tricuspid atresia, 1122-1123
indications for, 1174t, 2184
technical aspects of, 1195-1199
Atrial septum
anatomy of, 113
echocardiographic assessment of, 773, *773-774*, *779*
in atrioventricular canal defects, 1037-1038
left side of, 117, *118*
morphologic changes in, after birth, 131
Atrial situs. *See* Situs
Atrial switch operation. *See* Atrial baffle procedure(s)
Atrial tachycardia. *See* Atrial flutter; Supraventricular tachycardia
Atrial tracking
defined, 2152
Atriopeptin. *See* Atrial natriuretic factor
Atrioventricular block, 1800-1808
2:1, 1955
acquired
after cardiac trauma, 2538
after myocardial infarction, 2283
nonsurgical, 2137
autosomal-dominant, 2404
complete, 1802-1807, *1803*
sudden death and, 1914-1915
syncope in, 1934-1937
ventricular arrhythmias with, 1891
congenital
in neonatal lupus erythematosus, 1534, 1535, 1536
congenital complete, 1802-1806
anomalies associated with, 1908
clinical features of, 1804-1805
congestive heart failure due to, 2011, 2012
etiology of, 1803-1804
incidence of, 1803
indications for pacemaker in, 2136-2137, 2137t
pathology of, 1804, *1804-1805*
pregnancy with, 2382
prolonged Q-T interval and, 1890
response to exercise in, 1805, *1806*
sudden death and, 1915
syncope in, 1934-1935, *1938*
treatment of, 1805-1806
emergency management of, 2547t
exercise electrocardiography in assessment of, 1738-1740, *1739*
first-degree, 1800t, 1800
in fetus, 815-817, 1908
echocardiographic diagnosis of, 813, *814*, 815, *817-818*
in Lyme disease, 1538
intraoperative, 2298
second-degree, 1800-1802
clinical significance of, 1802
fetal, 1908
Mobitz Type I (Wenckebach), *1801*, 1801, 1802t, 1954-1955, *1955*
Mobitz Type II, 1801-1802
syncope in, 1934
treatment of, 1802
surgical, 1806-1807, *1807*, 2258
after tetralogy of Fallot repair, 2038
after ventricular septal defect repair, 1016, 2030
indications for pacemaker in, 2137
sudden death and, 1915
syncope in, 1934
syncope in, 1934-1937, *1938-1939*
Atrioventricular bundle. *See* His bundle
Atrioventricular canal, 80
septation of, 85-86, *87-88*
Atrioventricular canal defect(s), 1036-1051
acquired cardiovascular pathology associated with, 1040
angiographic assessment of, 957t, *1047-1048*, 1047-1048
blood flow in fetus with, 1040
bundle branch system anatomy with, 1787
cardiac catheterization in, 1045-1047
classification of, 1024, 1037
complete, 1039
defined, 1037
management of, 1966
prognosis in, 1050-1051
echocardiographic assessment of, 1042-1045, *1044*, *1046*
in fetus, 807, *809*, 810, *811*
with double-outlet right ventricle, *772*, 772
electrocardiographic findings in, 1042, *1042*
electrophysiology of, 1048
embryology of, 1037
history of, 1036-1037
in hypoplastic left heart syndrome, 1317, *1318*
natural history of, 1041
nuclear magnetic resonance imaging in, 862, 1045
partial
defined, 1037
prognosis in, 1049-1050
pathology of, 1037-1040
perimembranous ventricular septal defect vs., 773, *774*
physical examination in, 1041-1042
prognosis in, 1049-1051
radiographic findings in, 697, *701*, 1042, *1043*
radionuclide angiographic studies of, 1045
tetralogy of Fallot with, 1076
transitional forms of, 1038-1039
treatment of, 1048-1049
clinical caveats for surgery, 2299t

Atrioventricular canal defect(s), treatment of *(cont.)*
fragmentation hemolysis after patch repair, 2345
vasodilators for congestive heart failure with, 2094
with elevated pulmonary artery resistance
complications of repair of, 2263-2264
Atrioventricular connection
discordant. *See* Ventricular inversion
echocardiographic assessment of, 769-771, *770-771, 778*
in fetus, 808, *809-810*
univentricular. *See* Single ventricle
Atrioventricular dissociation
with junctional rhythm, 1954
with ventricular tachycardia, 1874, *1877*
Atrioventricular interval
defined, 2152
Atrioventricular nodal artery, 123, 125
Atrioventricular node, *113,* 123
age-related changes in, 125
development of, 104
evaluation of function of
on electrophysiology studies, *1746,* 1746
intraoperative injury to, 2258
location of, 113
with single ventricle, 1253-1255, 1256t
mesothelioma of, 1653
Atrioventricular ring, *103,* 104
Atrioventricular septal defect. *See* Atrioventricular canal defect(s)
Atrioventricular sulcus, 111
Atrioventricular valve(s). *See also* Mitral valve; Tricuspid valve
abnormalities of
ventricular inversion with, 1237
common
leaflet nomenclature for, 1038
echocardiographic assessment of, 773-774
in fetus, 807
formation of, 89, *92-93*
in atrioventricular canal defects, 1038
accessory orifices, 1039-1040
echocardiographic examination of, 1043-1044
insufficiency of. *See* Atrioventricular valve insufficiency
light microscopic features of, 128
offsetting of, 772
overriding of
embryology of, 1257
single ventricle and, 1248
straddling of
conduction system in, 1253-1255
embryology of, 1257
single ventricle and, 1248
Atrioventricular valve insufficiency. *See also* Mitral insufficiency; Tricuspid insufficiency
diagnosis of
in fetus, *821,* 821
in single ventricle, 1266
Atrium(-a). *See also* Left atrium; Right atrium
bilateral enlargement of
electrocardiographic findings in, *733,* 733
common
echocardiographic assessment of, in fetus, 807, *809*
in atrioventricular canal defects, 1039
isomyosins of, 218
septation of, 85, *85-86*
Atropine, 2554t
effects on pulmonary circulation, 374t, 376
in cardiopulmonary resuscitation, 411, 417
in parasympathetic neuronal function evaluation, 335
premedication with, 2291
succinylcholine with
for tracheal intubation, 2297
Attenuation
of ultrasound, *527,* 527
in various media, 525t
of x-rays, 628, 630
in biologic tissues, 630t
Augmentin (amoxicillin/clavulanic acid), 2053
Auricle. *See* Atrial appendage(s)
Auriculin. *See* Atrial natriuretic factor
Auscultation
blood pressure measurement by, 681
conditions for, 684-685
in cardiac physical examination, 684t, 684-689
in liver assessment, 2359
Auscultatory-electrocardiographic syndrome, 1974. *See also* Mitral valve prolapse
Austin Flint murmur, 688t, 1515-1516
rheumatic mitral stenosis vs., 1511
Autoantibody(-ies)
in postpericardiotomy syndrome, 1601
in rheumatic fever, 1487, 1489
in systemic lupus erythematosus, 1530
Autoimmune disease. *See also* Connective tissue disease(s); particular diseases
maternal
fetal atrioventricular block and, 815
Automaticity, 298-299, *299*
abnormal, 299, 311
mechanisms of arrhythmias due to, 314
altered normal
mechanisms of arrhythmias due to, 313
disease's effects on, 310-311
factors altering rate of, 299, 300t
in embryonic heart, 309
ionic basis of, 307, *308*
Autonomic nervous system
blockade and stimulation of
in sinus node function assessment, 1772
cardiovascular function regulation by, 325-328
development of, 328-330
disorders of. *See* Dysautonomia(s)
evaluation of, 330-335, 332t, 1943-1945
myocardial blood flow regulation by, 259-260
receptor physiology of, 318-324
Autoradiography
defined, 60
Autotransfusion device, 2261
Availability
of drugs, 471
Avascular necrosis of femoral head
in Down syndrome, 2456
Axial resistivity
effective, 301
Axillary vein
cannulation of
technique for, 950
cutdown to, 950
Axis deviation, 717-718, *720*
Ayre's T-piece
Jackson-Rees modification of, 2291, *2292*
Azathioprine
in heart transplantation management, 2235t, 2235, 2243-2244
Azlocillin, 2053
Azotemia
prerenal
diagnosis of, 2435t, 2435
Aztreonam, 2055-2056
Azygous vein, 1468
continuation of inferior vena cava by, 1468-1469
surgical significance of, 1469

B lymphocyte(s)
in humoral immune system, 2240
origin of, 2239-2240, *2240*
B_0
defined, 616
B1
defined, 616
Bache formula, *943,* 943t, 944
Bacteremia(s)
dentally-related
incidence of, 2350-2351, 2351t
gram-negative
infective endocarditis due to, 1570
in pathogenesis of infective endocarditis, 1562
antibiotic prophylaxis's effect on, 1566
dental procedures and, 676
procedures associated with, 1569t
Bacterial endocarditis. *See* Infective endocarditis
Bacterial infection(s). *See under* Infection(s)
Bacteriophage
defined, 60
Bactrim. *See* Trimethoprim-sulfamethoxazole
Baffes procedure, 1200
Balloon(s)
embolization, 1479, 2202
for valve dilation, *2189,* 2189
Balloon angioplasty, 2195-2201, *2197-2200*
coronary, 2284-2285
history of, 2280
in myocardial infarction management, 1718
for coarctation of the aorta, 1371-1372, *1372,* 1964, 2196-2197, *2197-2198*
for dialysis access stenosis, 993
for obstructed venous baffle, 2197-2198, *2199*
for pulmonary artery stenosis, 1413-1414, *1414,* 2198-2199, *2200*
in tetralogy of Fallot, 1088
for pulmonary vein stenosis, 1310, 2199-2201
for renal artery stenosis, *986,* 986, 2196
Balloon atrial septostomy. *See under* Atrial septostomy
Balloon counterpulsation. *See* Intra-aortic balloon counterpulsation
Balloon valvuloplasty, 2188-2195, *2189-2195*
double balloon technique, 2189, *2191*
for aortic stenosis, 1343
for rheumatic mitral stenosis, *1521,* 1521
valve measurement for, 2188
Ballooning mitral cusp syndrome. *See* Mitral valve prolapse
Barbiturate(s)
dosage adjustment for renal insufficiency, 2440t
syncope due to, 1941
Barium esophagography
in anomalous pulmonary artery diagnosis, 1445, *1445*
in anomalous right subclavian artery diagnosis, *1433,* 1440
in aortic arch anomaly diagnosis, 1433, *1434-1435,* 1441
Barlow's syndrome. *See* Mitral valve prolapse
Barometric pressure
altitude and, 441-442
Baroreceptor(s)
responses mediated by. *See* Baroreflex(es)
Baroreflex(es), 327

abnormal
conditions associated with, 335-336
evaluation of, *332*, 332-333
fetal development of, 329
Base of heart, 111
Base pair(s)
defined, 60
Battery(-ies)
pacemaker, 2141-2142
Bazett's formula, 723
Beam hardening, 637-638
Beam uniformity ratio (BUR), 527
Beau's lines, *2420*, 2420
Becker muscular dystrophy, 1676, 2318-2319, 2407
molecular basis of, 52-53
Beckwith-Wiedemann syndrome, 677, 2430t
molecular basis of, 54
Beer's law, 920
Behavior
type A
atherosclerosis and, 1992
Behcet's syndrome, 2418-2419
Benadryl (diphenhydramine), 2554t
Benign hypermobility syndrome, 2403, 2404t
Benzimidazole(s)
mechanisms of action of, 2068-2069
Benzodiazepine(s). *See also* Diazepam
dosage adjustment for renal insufficiency, 2440t
Beriberi, 1666-1667
Bernardinelli lipodystrophy syndrome
atherosclerosis in, 1993
Bernoulli effect
in pulmonary stenosis, 1392-1393
Bernoulli equation, 537
Beta blocker(s). *See also* particular drugs
antiarrhythmic effects of, 2127t, 2131-2132, 2551t
effects of
on delayed afterdepolarizations, 315
on pulmonary circulation, 374t, 375
in atrial flutter treatment, 1856-1857
in coronary artery disease management, 2285
in long Q-T syndrome management, 341, 342
in myocardial infarction management, 271, 1718
in ventricular arrhythmia management, 1899
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2364-2365
use of, in pregnancy, 2385, 2386t
verapamil interaction with, 2133
Beta$^-$ emission, 561
Beta-adrenergic agonist(s). *See also* particular agents
calcium channel regulation by, 305
effects on pulmonary circulation, 374t, 375
hypokalemic effect of, 2506
in pulmonary disease treatment
cardiac effects of, 2506
mechanisms of action of, 2067-2068, 2068t
use of, in pregnancy, 2385
Beta-adrenergic antagonist(s). *See* Beta blocker(s)
Beta-adrenergic receptor(s), *320*, 321t, 321
activity of, 328
desensitization of, 323
evaluation of responsiveness of, 334
inotropic agents' effects on, 2067-2068, 2068t
measurement of, 334-335
in syncope diagnosis, 1945
on pulmonary vessels, 362
regulation of, 323t, 323
in congestive heart failure, 341, 2073
role of, in myocardial contraction, 2066-2067, *2067*
Beta-lactamase inhibitor(s), 2053
Betamethasone
antenatal
effects on patent ductus arteriosus, 2118
Beta-oxidation, 195
Beta-pyridyl carbinol
infusion of
for myocardial protection, 270
Beta-transforming growth factor (TGFβ), 31
Bezold-Jarisch reflex, 327-328, 1715
Bias
Berksonian, 149-150
in research, 149-150, 645
information, 150
selection, 149-150
Biatrial enlargement
electrocardiographic findings in, *733*, 733
Bicarbonate concentration
renal regulation of, *460-461*, 460-462, 461t
Bicycle ergometer. *See also* Exercise testing
exercise testing with, 829t, 829
supine, 832
Bifascicular block, 1792-1794, *1793*
electrocardiographic findings in, 737, *738*
prognosis in, 1793-1794, 1794t
Bigeminy, *1956*, 1956
atrial, *1956*
blocked, 1956
fetal, 1907
rule of, 1872, 1956
ventricular, 1872-1874, *1873-1874*, *1956*
Bile acid(s)
cholesterol in, 479
enterohepatic circulation of, 479
Biliary atresia, 2362
Biliary colic, 1949
Biliary dysgenesis
intrahepatic
peripheral pulmonary stenosis and, 2362
Bilirubin
displacement of, from albumin
by diuretics, 2105
serum elevation of
in congestive heart failure, 2361
Billowing of posterior leaflet syndrome. *See* Mitral valve prolapse
Biophysical profile
for fetal assessment, 2392t, 2392
in hydrops fetalis management, 1906
Bishydroxycoumarin. *See* Dicumarol
Bit
defined, 657
Biventricular hypertrophy
electrocardiographic findings in, 731, *732*
Blade atrial septostomy. *See under* Atrial septostomy
Blalock-Hanlon operation
for single ventricle, 1270
for transposition of the great arteries, 1203
sinus node dysfunction after, 1776
Blalock-Taussig shunt, 2211
chest radiographic findings after, 694
for single ventricle, 1268-1270, *1270*
for tetralogy of Fallot, 1090-1091, *1091*
sequelae of corrective surgery after, *2038*, 2038
for transposition of the great arteries, 1203
for tricuspid atresia, 1123
neurologic complications of, 2312
nuclear magnetic resonance imaging of, 860
Blanking period, 2144
defined, 2153
Blastocyst, 72-73, *75-76*
Blebs
in no-reflow phenomenon, 268
Bleeding. *See* Hemorrhage(s)
Bloch, F., 570
Bloch equation(s), 577
defined, 616
Blood culture(s)
in infective endocarditis diagnosis, 1564-1565
techniques for, 2047-2048
Blood cyst(s)
on atrioventricular valves, 114
on semilunar valves, 117
Blood flow
across aortic valve
estimation of, 942t, 943
across mitral valve
estimation of, 943
across tricuspid valve
estimation of, 943
as morphogenetic influence, 166
carotid
cerebral blood flow vs., 408-409
cerebral. *See* Cerebral blood flow
distribution of
changes in response to exercise, 430-431, 431t
in fetus, 284
in newborn, 292
disturbed, *537*, 537, 598
echocardiographic assessment of. *See* Doppler echocardiography
effects of, on nuclear magnetic resonance imaging, 598-600, *599-601*
fetal
age-related changes in, 822-823
distribution of, 284
redistribution of, in response to stress, 284, 286
laminar, 536, 598
flow disturbance and, *537*, 537
measurement of, 494-499
by Doppler echocardiography, 497-498, 793-796
by nuclear magnetic resonance, 498, 602
by positron emission tomography, 497, 621-622
in atrioventricular canal defect, 1046
in embryo, 166
invasive techniques for, 495-497
noninvasive techniques for, 497-498
semi-invasive techniques for, 497
terminally invasive techniques for, 494-495
myocardial. *See* Myocardial blood flow
nuclear magnetic resonance artifact due to, 609-610
reduction techniques for, 601-602
patterns of, 536-537, 598
physics of, *536-537*, 536-537
plug, 598
pulmonary. *See* Pulmonary blood flow
regional
in cardiopulmonary resuscitation, 407-409, *408-409*
renal. *See* Renal blood flow
spatial velocity profile of, *536*, 536
turbulent, 536-537, 598
murmurs and, 1919-1920

Blood flow *(cont.)*
umbilical
Doppler assessment of, 822, *824-825*
regulation of, 282
uterine
fetal regulation of, 281-282
maternal regulation of, 281
velocity of
flow volume and, 498, *537*, 537
pressure gradient determination from, 537
Blood gas method
oxygen saturation calculation from, 920
Blood pool imaging, 837-843
blood flow measurement using, 497
clinical indications for, 841-843
during exercise testing, 832
equilibrium method (multiple gated acquisition), 837-840, *838-839*
first-pass method, 840-841, *841-842*
in coronary artery disease diagnosis, 2284
instrumentation for, 837-838, *838*
methods compared, 837t
safety of, in pregnancy, 2377
Blood pressure. *See also* Hypertension; Hypotension
as afterload measurement, 236
changes in, in pregnancy, 2375
clinical methods of recording, 681t
heart rate response to changes in
in baroreflex evaluation, 333
in clinical assessment of heart disease, 681-682
measurement of
by auscultation, 681
by Doppler ultrasound, 681
by flush technique, 682
by oscillometric method, 493, 681-682
by palpation, 681
cuff size and, 681
during anesthesia, 2295
during cardiac catheterization, 918, 947
during exercise testing, 830-831
in embryo, 165-166
invasive, 492-493
noninvasive, 493
Blood volume. *See also* Hypovolemia
changes in
in pregnancy, 2375
in weightless environment, 437, 438
Blueberry muffin baby, *2421*, 2421
Body surface mapping, 518-520, *519-520*
Body temperature. *See also* Hypothermia
control of, during cardiac catheterization, 948-949
monitoring of, during anesthesia, 2296-2297
Boltzmann distribution
defined, 616
Bombesin
in fetal lung, 362
Bone cyst
aneurysmal
embolization for, 992
Bone marrow
chloramphenicol's effects on, 2058
chromosomal analysis using, 178
Bone marrow transplantation
cardiac complications associated with, 2342
cyclophosphamide and, 2341, 2342
Bonferroni adjustment, 652
Bonnevie-Ullrich syndrome, 188
Boosted antibody response, 2240
Boot-shaped heart, 703, *1081*, 1081
Borrelia burgdorferi, 1538. *See also* Lyme disease
Bourneville-Pringle disease. *See* Tuberous sclerosis
Brachial artery
cannulation of
for blood pressure monitoring during anesthesia, 2295
systolic pressure in, 918
Brachial radiculoplexopathy
due to cardiac surgery, 2313
Brachial vein cannulation
technique for, 950
Bradycardia. *See also* Tachycardia-bradycardia syndrome
fetal, 813, 815, 1907
defined, 1905
echocardiographic diagnosis of, 814
intraoperative, 2298
pacing for
transthoracic, 2171-2172
with implanted pacemaker, 2135-2155
postoperative, 2257-2258
sinus. *See* Sinus bradycardia
sudden death and, 1912
symptoms of, 1726
ventricular arrhythmias with, 1891
Bradykinin, 464
effects on pulmonary circulation, 374t, 376-377
mechanisms of, 366
in regulation of ductus arteriosus closure, 2110
inactivation of
in lungs, 365
postnatal drop in pulmonary vascular resistance and, 363
Brady/tachyarrhythmia(s), 1759-1760, *1761-1763*
Brain abscess, 2308-2310, 2464-2467
cerebrovascular accident vs., 2308, 2309, 2454
clinical manifestations of, 676, 2308, 2466
complications of, 2310, 2467
culture techniques for microorganisms in, 2047, 2309
diagnosis of, 2308-2309, *2309*, 2466, *2467*
differential diagnosis of, 2309, 2466t, 2466
epidemiology of, 2464-2465, 2465t
etiologic agents of, 2465t, 2465
in right-to-left shunt, 1072
in tetralogy of Fallot, 1089
in tricuspid atresia, 1121
management of, 2309-2310, 2466-2467
pathogenesis of, 2308, 2454, 2465-2466
pathologic findings in, *2309*, 2309
Brainstem
cerebrovascular accident involving deficits associated with, 2305
Branching enzyme deficiency
in Andersen disease, 1665
Breast(s)
pain originating in, 1948
Breath-holding spell(s), 2323
sinus node dysfunction and, 1775
Breathing. *See* Respiration; Ventilation
Bremsstrahlung, 552, 553, *563*, 563
Brescia-Cimino internal fistula, 992
Bretylium, 2127t, 2132, 2551t
dosage adjustment for renal insufficiency, 2441t
for ventricular fibrillation, 1900-1901
in cardiopulmonary resuscitation, 419-420
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2366
ventricular tachycardia and, 1898
Brockenbrough effect
in hypertrophic cardiomyopathy, 1632
Bromocriptine
hypoadrenergic dysautonomia due to, 340
Bronchial artery(-ies), 362
Bronchial embolization
transcatheter, 978, *979*
Bronchodilator(s). *See also* particular drugs
cardiac effects of, 2506
for cor pulmonale, 2505
Bronchopulmonary sequestration, 976-978, *977*, 2508
Bronchus(-i)
external compression of
in anomalous left pulmonary artery, 1444-1447
in left-to-right shunt lesions, 2506-2507
obstruction of
in left-to-right shunt lesions, 2507
Brucella
culture techniques for, 2048
Bucky grid (antiscatter grid), 555, 638
Bucrylate
transcatheter embolic therapy with, 1479
Buffer(s)
function of, 460
Bulbar septum. *See* Ventricular septum, outlet
Bulboatrioventricular flange, 81
Bulboatrioventricular ledge, 81
Bulbotruncal ring, *103*
Bulboventricular flange, 81
Bulboventricular foramen, 81
in single ventricle, 1249
Bulboventricular groove, 81
Bulboventricular ledge, 81
Bulboventricular ring, *103*
Bulboventricular septum
formation of, 86-87, *89*
Bulbus cordis, 81
Bulimia
ipecac abuse in, 1673
Bulk magnetization vector (M), *573*, 573-574
deflection of, 575
equation of motion of, 577
Bumetanide (Bumex), 2103, 2548t
dosage adjustment for renal insufficiency, 2441t
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2366
Bumex. *See* Bumetanide
Bundle branch block, 1786-1799. *See also* Left bundle branch block; Right bundle branch block
electrophysiologic testing in evaluation of, 1796-1797
rate-dependent, 1795, *1795-1796*
supraventricular tachycardia with, 1830-1831, *1832*
Bundle of His. *See* His bundle
Bundle of Kent. *See* Kent bundle
Burger's scalene triangle, 504, *506*
Busulfan
cardiotoxicity of, 2341
Butyrophenone
in Sydenham's chorea management, 1499
Bypass tract(s). *See also* Kent bundle; Lown-Ganong-Levine syndrome; Mahaim fiber(s); Wolff-Parkinson-White syndrome
supraventricular tachycardia with, 1837-1842, *1839*
Bypyridine(s). *See also* particular drugs
mechanisms of action of, 2068
Byte
defined, 639, 657

C protein, 213
Cachexia
  cardiac, 2355
Cadherin group, 156
Café-au-lait spot(s)
  in neurofibromatosis, 2416
Caffeine
  effect on delayed afterdepolarizations, 315
  inotropic effects of, 2068
  stimulation of calcium release by, 206
Calcium
  accumulation of
    in myocardial ischemia, 1690
  agents altering myocardial sensitivity to, 2068-2069
  in actomyosin complex regulation, 215
  in cardiopulmonary resuscitation, 418
  in myocardial contraction, 203, *203-204,* 2066, *2067*
    historical background of, 202-203
  in regulation of ductus arteriosus closure, 2109
  myocardial cellular movements of, 202-211
    acetylcholine's effects on, 321
    across mitochondrial membranes, 207-208
    across sarcolemma, 204-205, 205t
    across sarcoplasmic reticulum, 205-207
    alterations in, in congestive heart failure, 247-248, *248*
    during development, 208-209, *210*
  proteins regulating cytosolic concentrations of, 41-42
  release of
    alpha-adrenergic agonists in, 320
  resting membrane potential and, 295
  serum levels of. *See* Hypercalcemia; Hypocalcemia
  troponin binding of, 214
  tubular transport of, 454
  urinary excretion of
    in neonate, 465
Calcium adenosinetriphosphatase
  of sarcolemma, 205t, 205, 209t
  of sarcoplasmic reticulum, 41, 206t, 206-207, 209t
    during development, 209
Calcium channel(s)
  characteristics of, 304-306
  high-threshold, 304-305
  low-threshold, 304-305
  of sarcolemma, 204
    during development, 208
  of sarcoplasmic reticulum, 206t, 206
    during development, 209
  regulation of, 305
Calcium channel blocker(s). *See also* particular drugs
  as antiarrhythmic agents, 2133, 2551t-2552t
    for atrial flutter, 1857
    for ventricular arrhythmias, 1899
  as cardioplegic agents, 272-273
  effects of
    on delayed afterdepolarizations, 315
    on pulmonary circulation, 374t, 378-379
  for cor pulmonale, 2505
  for hypertrophic cardiomyopathy, 1633
  for myocardial protection, 271
  for pulmonary hypertension, 2002-2003
  in cardiopulmonary resuscitation, 418
  mechanisms of action of, 305
  pharmacology of
    in hepatic, gastrointestinal or nutritional disorders, 2366
Calcium chloride, 2553t
Calcium gluconate, 2553t
Calcium paradox, 208, 268-269
Calibration spike
  on electrocardiographic system
    artifact due to, 758, *759*
Calmodulin
  calcium adenosinetriphosphatase of sarcolemma and, 205
Calsequestrin, 206t, 207
Camera(s)
  gamma. *See* Gamma camera(s)
  television
    in digital subtraction angiography, 639
cAMP. *See* Cyclic adenosine monophosphate
Canal(s) of Lambert, 350
Canalis atrioventricularis communis. *See* Atrioventricular canal defect(s)
Candida spp.
  infective endocarditis due to, 1570
Cannon wave, 682
Cannulation. *See* Arterial cannulation; Venous cannulation
Cap
  defined, 61
Capacitance
  defined, 502
  membrane
    conduction velocity and, 301
Capillary angioma, 1472-1473, *1474-1475*
Captopril (Capoten), 2434t, 2549t
  dosage adjustment for renal insufficiency, 2440t
  effects on pulmonary circulation, 374t, 378
  food's effect on absorption of, 2367
  for congestive cardiomyopathy, 1623, 2091-2092
  for congestive heart failure, 2019, 2020t
  for postoperative heart failure, 2095
  in myocardial infarction management, 1717
  liver dysfunction due to, 2368
  pharmacology of, 2088t, 2089-2090, 2364t
    in hepatic, gastrointestinal or nutritional disorders, 2367
  use of, during pregnancy, 2387t
Capture
  pacemaker
    defined, 2153
Carbamazepine
  hypoadrenergic dysautonomia due to, 340
Carbapenem(s), 2056
Carbenicillin, 2053
  dosage adjustment for renal insufficiency, 2440t
Carbicarb
  for metabolic acidosis with cardiac arrest, 417
Carbohydrate(s)
  absorption of
    in heart disease, 2358
  metabolism of, 192-194
    kidney in, 463
Carbon dioxide
  arterial partial pressure (Pa_{CO2})
    in respiratory control during exercise, 431-432
    set point of, 431-432
  exchange of, across placenta, 282
  in metabolic regulation of myocardial blood flow, 258
  production of
    from lactic acid buffering, 431
Carbon dioxide rebreathing method
  for cardiac output measurement, 832
Carbon-11
  positron emission tomography using, 620
Carbon-13
  nuclear magnetic resonance spectroscopy using, 615
Carbonic acid-bicarbonate buffer system, 460-462
Carbonic anhydrase
  endothelial
    activity of, in lungs, 366
Carbonic anhydrase inhibitor(s), 2106
Carboxypeptidase N
  activity of, in lungs, 366
Carcinoid disease of bowel
  pulmonary stenosis in, 1397
Carcinoma
  hepatocellular, 981
Cardiac assist device(s)
  for failure to wean from cardiopulmonary bypass, 2303
Cardiac cachexia, 2355
Cardiac catheterization, 913-945
  adolescent's and young adult's perceptions of, 2523-2524
  assessment prior to, 947-948
  clinical applications of, 946-967
  complications of, 963-966
    neurologic, 2312
    orthopedic sequelae of, 2451-2453, *2453*
  drugs used with, 963
    emergency, 963, 964t
  guidelines for laboratory, 556-557, 557t
  hemodynamic measurements during, 947
    sequence for, 913, 914t
  hemostasis and anticoagulants in, 962
  historical background of, 946-947
  imaging with, 951-952
  in anemic patients, 962
  in neonate, 1190-1192
    patient transport to laboratory for, 948-949
  in polycythemic patients, 962-963
  indications for, 947t, 947
  indicator dilution curves in, 933-939
  left heart techniques, 951
    retrograde, 951
    transseptal, 951
  monitoring during, 949
  mortality from, 963-965
  oximetry in, 919-926
  oxygen consumption measurement in, 927-929
  premedication for, 948
    adverse reaction to, 2312
  pressure data collection in, 915-919
    frequency response in, 915
    procedure for, 915-916
  right heart techniques, 949-950
  safety of, in pregnancy, 2377
  therapeutic, 2183-2209
    dilation techniques, 2183-2201
    future of, 2208
    occlusion techniques, 2201-2208
  thermodilution in, 939-940
  vascular resistance calculation in, 929-933
Cardiac cycle
  high-energy phosphate metabolite levels and nuclear magnetic resonance studies of, 615
Cardiac failure. *See* Heart failure
Cardiac function. *See under* Heart
Cardiac glycoside(s). *See also* particular drugs
  clinical use of, 2071-2072
  inotropic effect of
    sodium-calcium exchanger in, 205
  mechanisms of action of, 2068
  pharmacology of, 2071

Cardiac hypertrophy. *See also* Ventricular hypertrophy
contractile protein composition changes in, 36-37, 246
coronary vascular reserve in, 262
in compensation of congestive cardiac failure, 246-247
nuclear magnetic resonance studies of, 615
proto-oncogene induction in, 41
Cardiac index
calculation of
by Fick method, 496
Cardiac jelly, 79, 82
cardiac looping and, 156-157
in endocardial-mesenchymal migration, 160
Cardiac lipidosis
isolated. *See* Ventricular tachycardia, incessant, in infants
Cardiac looping, 81-82, *83,* 156-158, 1234-1236, *1235-1236,* 1280
Cardiac malposition, 1280-1287. *See also* Dextrocardia
defined, 1280
electrocardiographic findings in, 724-727
terminology of, 1280-1282
Cardiac metabolism. *See under* Metabolism
Cardiac muscle
development of
ultrastructural and cell culture studies of, 30
functional maturation of
molecular basis of, 32-42
resting tension of, *234,* 234
Cardiac output, 231
changes in, in pregnancy, 2374-2375
defined, 927
developmental changes in, 239-241, *240-241*
exercise's effects on, 430
heart rate's effects on, 239
in fetus
determinants of, 284
in newborn, *292,* 292
low
after myocardial infarction, 2283
compensatory mechanisms in, 2086-2087
emergency management of, in infancy, 2543t
syncope due to, 1930-1931
measurement of
by cine-CT scanning, 882, 883
by Doppler echocardiography, 794-795, *796-797*
by equilibrium blood pool imaging, 839
by first-pass blood pool imaging, 841
by indicator dilution method, 496, 934-937, *935-937,* 936t
by thermodilution method, 939-940, *940*
during exercise testing, 832, 833, *833*
in embryo, 165
normal values for, 927
oxygen consumption and, 832
postoperative
assessment of, 2255
heart rate and, 2257-2258
methods for improvement of, 2255-2257
preload, afterload and contractility's effects on, 237-239, *237-239*
redistribution of
in compensation of congestive cardiac failure, 246
Cardiac plexus(es), 127
Cardiac rehabilitation, 2267-2273
assessment of results of, 2271-2273, 2272t
athletic participation after, 2272-2273, 2273t
benefits of, 2267-2268
conduct of, 2270-2271, 2271t
continuing fitness program after, 2272-2273
contraindications to, 2267, 2270
defined, 2267
electrocardiographic monitoring during sessions of, 2271
equipment for, 2269-2270
home-based, 2269
personnel for, 2268-2269
physical setting for, 2269-2270
supervision needed during, 2268-2269
third-party payment for, 2269
Cardiac rupture, 2536-2537
Cardiac surgery. *See also* particular procedures and under particular disorders
care after. *See* Postoperative care
chylothorax after, 2264, 2512-2513
complications of, 2024-2043
defined, 2025
hemostatic, 2343t, 2343-2344
intraoperative, 2298
neurologic, 2258, 2312-2314
renal, 2433-2439
decisions and techniques in, 2210-2226
during pregnancy, 2387
in diabetes, 2496
parental attitudes after, 2520-2521
pregnancy after, 2382
preparation for, 2290-2293
residua and sequelae of, 2024-2043
Cardiac tamponade
in juvenile rheumatoid arthritis, 1528
management of, 1529
in pericarditis, 1592
postoperative, 2257
treatment of, 1596-1597
Cardiac transplantation, 2227-2238
accelerated atherosclerosis after, 1993, 2237, 2280
antidiuretic hormone regulation after, 2495
contraindications to, 2228
cost of, 2229-2230
donor management for, 2230-2231
donor selection for, 2230
experience with, 2236-2237
for hypoplastic left heart syndrome, 1329-1331
for idiopathic dilated cardiomyopathy, 1624
future directions in, 2237
history of, 2227-2228
human leukocyte antigens in, 2241
immunization recommendations with, 2473
immunosuppression after, 2235t, 2235, *2243-2244,* 2243-2244
indications for, 2228
infection after, 2244-2245, 2246t, 2467-2468, *2468*
long-term consequences of, 2239-2250
malignancy after, 2245-2247, 2246t, *2248*
National Recipient Waiting List for, 2230
neurologic complications of, 2314-2315
nuclear magnetic resonance imaging in, 864
postoperative care in, 2234-2235
recipient evaluation for, 2228-2230, 2229t
rejection after. *See* Rejection
steroid therapy after, 2235, 2244, 2497-2498
surgical techniques for, 2231-2234, *2232-2233*
donor procurement operation, 2231
recipient operation, 2231-2234
xenograft, 2237
Cardiac vein(s), 126
Cardinal vein(s), 99-103, *101,* 1462-1463, *1464*
Cardioaccelerator function, 333
Cardioauditory syndrome. *See* Jervell-Lange-Nielsen syndrome
Cardiocyte(s)
atrial, 2496
Cardiofacial syndrome, 2429t
Cardiolipin
antibodies to
in systemic lupus erythematosus, 1530
Cardiologist
role in cardiac rehabilitation program, 2268
Cardiomyopathy(-ies), 1617-1646
arrhythmogenic, 1636-1641. *See also* Arrhythmogenic right ventricular dysplasia
blood pool imaging in assessment of, 843
congestive. *See* Dilated cardiomyopathy
definition and classification of, 1617-1618, 1618t-1619t
dilated. *See* Dilated cardiomyopathy
focal lipid. *See* Ventricular tachycardia, incessant, in infants
histiocytoid. *See* Ventricular tachycardia, incessant, in infants
hypertrophic. *See* Hypertrophic cardiomyopathy
hypoxic neonatal, 2479-2480
idiopathic infantile. *See* Ventricular tachycardia, incessant, in infants
infantile xanthomatous. *See* Ventricular tachycardia, incessant, in infants
molecular basis of, 54, 57
nondilated (restrictive), 1634-1636
characteristics of, 1617, 1619t
constrictive pericarditis vs., 1598
etiology of, 1634t, 1634-1635
oncocytic. *See* Ventricular tachycardia, incessant, in infants
peripartum, 2378
positron emission tomography studies in, 875-876
post-asphyxial, 2479-2480
primary
classification of, 1617, 1619t
secondary, 1617, 1618t
X-linked
molecular basis of, 54
X-linked recessive
gene therapy for, 59
Cardionatrin. *See* Atrial natriuretic factor
Cardioplegia, 272-273
development of, 272
solutions for, 2301t, 2301, 2302
Cardiopulmonary bypass, 2210-2211, 2299-2303
anticoagulation and reversal in, 2300
conduct of, 2301-2302, *2302*
hematocrit during, 2300
hemostatic alterations created by, 2344
hypothermia and circulatory arrest with, 2302
in cardiopulmonary resuscitation, 423-424
myocardial preservation during, 2302
oxygenators for, 2299-2300
perfusion pressure during, 2301
postoperative respiratory function and, 2253
priming extracorporeal circuit for, 2300-2301
pumps for, *2299,* 2299
weaning from, 2302-2303, 2303t
Cardiopulmonary resuscitation (CPR), 401-427
arterial and venous blood gas differences in, 416
cough, 406, *407*
drugs used in, 409-420
in children, 402t

in neonates, 403t
in operating room, 2293t, 2293
route of administration, 409-410
experimental methods of, 422-424
external compression, 406
in children, 404t-405t
drugs used in, 402t
outcome of, 402-406, 406t
in neonates, 2478
drugs used in, 403t
outcome of, 406
interposed abdominal compression (IAC-CPR), 423
intrathoracic pressure model of, 406-407
mechanism of circulation during, 406-407, *407-408*
outcome of, 401-406
in adults, 401-402
in children, 402-406, 406t
in neonates, 406
pacemaker therapy for, 422
preparation for
in exercise laboratory, 830
in operating room, 2293t, 2293
pump theory of, 406
regional blood flow in, 407-409, *408-409*
simultaneous ventilation and compression (SVC-CPR), 422-423, *423*
Cardiothoracic ratio
in congestive heart failure diagnosis, 2009
of infant, 692
Cardiotomy suction, 2301
Cardiotoxin(s), 1672-1674. *See also* particular toxins
Cardiovascular disease(s). *See also* particular diseases
manifestations of, 2026t
molecular basis of, 42-57
potential consequences of, 2026t
Cardiovascular reflex(es), 327-328
development of
in childhood, 330
in fetus, 328-329
in neonate, 329-330
receptor modulation of, 328
tests of, 331-335, 332t
Cardiovascular reflex arc(s), 325-326
components of, 326-327
Cardiovascular status
factors causing alterations in
in cardiac catheterization patient, 913-914
Cardiovascular system. *See also* particular structures
altitude's effects on, 442-443, 443t
anatomy of. *See* Anatomy
development of
in space, 438-439
molecular genetics of, 3-70
Cardioversion, 2167
clinical applications of, 2171
complications of, 2169-2170
energy requirements for
paddle location and, 2169
for atrial flutter, *1857,* 1857, 2171
for pacemaker patient, 2170
for supraventricular tachycardia, 1822, 2171
atrial pacing vs., 2164-2165
in digitalis toxicity, 2169-2170
method of, 2170
transvenous, 2171
Carditis
differential diagnosis of, 1497-1498
in rheumatic fever, 1490-1491, 1492-1493
incidence of, 1498
Carey-Coombs murmur, 688t
in rheumatic mitral valvulitis, 1493, 1502
Carnegie stage(s), 72, 73t
L-Carnitine
infusion of
for myocardial protection, 270
Carnitine deficiency, 1667-1668
endocardial fibroelastosis vs., 1626
primary muscle, 2321
primary systemic, 2321
Carotid artery(-ies)
formation of, 93
left
normal anatomy of, 1425
origin of, 96
resistance of, to transmural pressure, 407
Carotid blood flow
cerebral blood flow vs., 408-409
Carotid chemoreceptor(s)
diving reflex and, 335
in control of breathing, 358
Carotid sinus hypersensitivity, 335-336
atropine in evaluation of, 335
sinus node dysfunction and, 1775
Carotid sinus massage
in supraventricular tachycardia treatment, 1821
in syncope diagnosis, 1945
parasympathetic blockade with, 335
Carotid sinus stripping procedure, 336
Carpenter's syndrome, 677t-678t, 678
Carter formula, *938,* 938
Case-control study design, 145t, 146-147
Case-series study design, 144, 145t
Castle, Winifred
on statistical analysis, 648
Catalase
effects on postischemic dysfunction, 274
for myocardial protection, 271
Catapres. *See* Clonidine
Catecholamine(s). *See also* particular catecholamines
cardiovascular effects of excessive release of, 1671
measurement of, in syncope diagnosis, 1943-1944
protein degradation and, 199
Cat-eye syndrome, 188
cardiac and renal anomalies in, 2429t
Catheter(s)
balloon septostomy, 1195-1196, *1196,* 2184
balloon-flotation, 914-915, 950
perforation of heart and, 965
preformed curve in, 1192
blade septostomy, 1197-1199, *1199,* 2185, *2186*
central venous
chylothorax due to, 2513
infections involving, 2462-2463
for cardiac catheterization, 913, 914-915, 950
for peripheral vascular angiography, 973-974, *974*
for selective coronary arteriography, 969
for transesophageal pacing, 2166
manometer-tipped, 915-916, *916*
Swan-Ganz. *See* Pulmonary artery catheter(s)
Catheter ablation, 1749, 1895
Catheter embolization. *See under* Embolization
Catheter impact artifact, 916
Catheter whip artifact, 916
Cathode-ray oscilloscope
electrocardiograph using, 511-512, *513*
Cavitation(s)
ultrasound and, 781, 825
Cayler syndrome, 2429t
CCAAT box associated repeat (CBAR)
in actin genes, 39-40
Cefaclor (Ceclor), 2054
Cefadroxil (Duricef; Ultracef), 2054
Cefazolin (Ancef; Kefzol), 2053-2054
dosage adjustment for renal insufficiency, 2440t
parenteral dosage for severe infection, 2057t
Cefizox (ceftizoxime), 2055
Cefoperazone (Cefobid), 2055
Cefotaxime (Claforan), 2054-2055
dosage adjustment for renal insufficiency, 2440t
in brain abscess treatment, 2467
parenteral dosage for severe infection, 2057t
Cefoxitin (Mefoxin), 2054
dosage adjustment for renal insufficiency, 2440t
Ceftazidime (Fortaz; Tazicef), 2055
dosage adjustment for renal insufficiency, 2440t
parenteral dosage for severe infection, 2057t
Ceftizoxime (Cefizox), 2055
Ceftriaxone (Rocephin), 2055
dosage adjustment for renal insufficiency, 2440t
parenteral dosage for severe infection, 2057t
Cefuroxime (Zinacef), 2054
dosage adjustment for renal insufficiency, 2440t
parenteral dosage for severe infection, 2057t
Celiac disease
pharmacokinetics of beta blockers in, 2365
Cell culture studies
limitations of, 368-369
Cell death
in development, 164-165
Cell membrane
electrical model of, *300,* 300-301
Cell migration, 152-154, *155*
mechanisms of, 154-156, *156-157*
Centimorgan (cM)
defined, 61
Central fibrous body, 111, *112*
Central nervous system
in control of breathing, 357
injury to
effects on electrocardiogram, 752
pulmonary edema following, 398
postoperative assessment of, 2258-2259
Central tendency
measures of, 648
Central venous cannulation, 2296
Central venous catheter(s)
chylothorax due to, 2513
infections involving, 2462-2463
Centronuclear myopathy, 1677, 2321
Cephalexin (Keflex), 2053
Cephalosporin(s), 2053-2055. *See also* particular drugs
dosage adjustment for renal insufficiency, 2440t
penicillin allergy and, 2049
structure of, *2051*
Cephalothin (Keflin), 2053
dosage adjustment for renal insufficiency, 2440t
Cerebral abscess. *See* Brain abscess
Cerebral aneurysm(s). *See under* Aneurysm(s)
Cerebral blood flow
altitude and, 444
carotid blood flow vs., 408-409
in cardiopulmonary resuscitation, 408-409, *409*
Cerebral cortex
in control of breathing, 357

Cerebral edema
high altitude, 445, 446
pathologic findings in, *2315*
treatment of, 2315
with abscess
management of, 2309-2310
Cerebral embolism. *See under* Embolism
Cerebral hemorrhage. *See* Intracranial hemorrhage
Cerebral thrombosis. *See under* Thrombosis
Cerebrovascular accident(s), 675-676, 2305-2308
causes of, 2307t
cerebral abscess vs., 2308, 2309
differential diagnosis of, 2306
during or after cardiac catheterization, 1202
in coarctation of the aorta, 2311
in tetralogy of Fallot, 1089
in transposition of the great arteries, 1201-1202
laboratory findings and diagnostic evaluation of, *2306,* 2306
orthopedic sequelae of, 2453-2455
pathogenesis of, 2305
pathologic findings in, 2306, *2307*
symptoms and signs of, 2305
timing of heart surgery after, 2308
treatment and prognosis in, 2306-2308
Cesarean section
indications for, 2375-2376
Chagas' disease, 1582, 2472
Charcot-Marie-Tooth disease
orthopedic problems in, 2458
Chargaff's rules, *4,* 4
CHARGE association, 2411, 2430t
Charting
computer programs for, 664, *665*
Chediak-Higashi syndrome
atherosclerosis in, 1993
Chemical cleavage method, 9, *10*
Chemical shift
defined, 616
in nuclear magnetic resonance imaging
artifact due to, 609, *610*
fat and water image formation using, 871
in nuclear magnetic resonance spectroscopy, *610,* 610-611
Chemoreceptor(s)
carotid
diving reflex and, 335
in control of breathing, 358
responses mediated by, 327-328
Chemotherapy. *See also* particular drugs and classes of drugs
cardiotoxicity of agents used in, 2338-2341
intra-arterial
for osteosarcoma, 992
maternal exposure to
hematologic and oncologic problems in child after, 2330
Chest compression
for asphyxiated neonate, 2478
Chest massage
electrocardiographic artifact due to, 758
Chest pain, 675, 1947-1950
benign adolescent, 1950
cardiac, 1949
causes of
in children, 1685, 1697
psychogenic, 1949
noncardiac, 1947-1949
studies in diagnosis of, 1949-1950
Chest percussion
electrocardiographic artifact due to, *758,* 758
Chest syndrome
in sickle cell disease, 2334
Chest tube
position of
after surgery for congenital heart disease, 711
Chest wall
chest pain originating in, 1948
compliance of, 351-352
deformities of
cor pulmonale due to, 2504
mechanics of, 354-355
during sleep, 354
muscles of, 354-355
Chiari net, 113
Chick embryo, 152
Chickenpox. *See* Varicella
Chi-square test, 647t, 653
Chloral hydrate, 2553t
Chloramphenicol, 2057-2058
adverse effects of, 2058
in liver disease, 2049
in neonates, 2048
for brain abscess, 2467
for Haemophilus influenzae infection, 2469
parenteral dosage for severe infection, 2057t
Chloride
in tubular fluid
renin release and, 463
Chloroform
effects on electrocardiogram, 751
Chloroquine
cardiotoxicity from, 1663-1664
Chlorothalidone
pharmacokinetics of, 2104
Chlorothiazide (Diuril), 2434t, 2548t. *See also* Diuretic(s), thiazide
dosage of, 2102t
for congestive heart failure, 2016
pharmacokinetics of, 2104, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2366
Chlorpromazine (Thorazine), 2553t
premedication with
for cardiac catheterization, 948
Cholelithiasis
neonatal
furosemide therapy and, 2103
Cholera toxin
effects on adenyl cyclase activity, 322
Cholesterol, 475
blood levels of
coronary artery disease risk and, 1991, 2281
deposits of, in atherosclerosis
smooth muscle proliferation and, 488
diet and, 479
esterification of, 475-476
metabolism of, 478-480, *479-480*
in atherosclerosis, 482
screening for
in children, 1988
Cholesteryl ester, 475-476
Cholesteryl ester storage disease, 1662
molecular basis of, 47
Cholestyramine
digoxin interaction with, 2363
drug absorption and, 2367
Cholinergic mechanism
in regulation of ductus arteriosus closure, 2110
Cholinergic receptor(s), 321-322, *322*
Chondroectodermal dysplasia. *See* Ellis-van Creveld syndrome
Chondroitin sulfate
in endocardial-mesenchymal migration, 160, *162*
Chorda(e) tendinea(e)
of left ventricle, 118
of right ventricle, 114
Chorea
in rheumatic fever. *See* Sydenham's chorea
Choreoathetosis
after hypothermia, 2041, 2313
Chorionic cavity, 73
Chorionic villus, *281,* 281
Chorionic villus sampling, 20, 178
Chromatin, 17
conformation of
gene activation and, 17
Chromosomal abnormality(-ies), 171-190. *See also* particular disorders
congenital heart defects with, 179t-180t
types of, 176-177
with hematologic and cardiovascular consequences, 2328-2330, 2329t
with orthopedic and cardiovascular involvement, 2456
Chromosomal library
defined, 61
Chromosome(s), 176
abnormalities of. *See* Chromosomal abnormality(-ies); particular disorders
analysis of, 178t, 178-179
banding of, 176, 178
classification of, 176
duplication of, 177
nomenclature of, 177-178
of eukaryotic cells, 15
pairing of, 11-12
structure of, 17
translocation of, *14,* 14, 177
Chromosome jumping, *29,* 29
Chromosome walking, 10, *13,* 29
defined, 61
Chyloma, 2513
Chylomicron(s)
defined, 61
in lipid transport, 477-478, *478*
Chylomicronemia, 478
Chylothorax, 2512-2514
postoperative, 2264
after coarctation repair, 1370
after surgical ligation of patent ductus arteriosus, 2027
Cigarette smoking. *See* Smoking
Cilastatin
imipenem with, 2056
Cimetidine
dosage adjustment for renal insufficiency, 2441t
drug interactions with, 2367
Circle of Vieussens, 125, 1453
Circle system, 2291, *2293*
Circulation
bronchial, 362
changes in
with altitude, 442-443
fetal, 283-284, *284,* 805-806
delayed transition from, at altitude, 446
functional anatomy of, 283, *284*
mechanisms of control of, 287
persistent. *See* Persistent pulmonary hypertension of newborn
responses of, to stress, 286-287
shunt pathways in, 283-284, *284*
fetal-placental, 280-282
mechanism of
during cardiopulmonary resuscitation, 406-407, *407-408*

pulmonary, 360-385
anatomy of, 386
development of, 96-98, *97-98,* 362-364
functions of, 364-365
pharmacologic agents' effects on, 373-379, 374t
structural modifications of, with congenital heart defects, 364
transitional, 285-286, *286*
volume of blood in, 364
transitional, 284-286, *285-286,* 2477-2478
umbilical
regulation of, 282
Circulatory arrest
duration of
neurologic complications and, 2312
hypothermia with, 2302
Cirrhosis
cardiac, 2359-2360
Cis-platinum
cardiotoxicity of, 2341
Citric acid cycle, *196,* 196
Claforan. *See* Cefotaxime
Clathrin(s), 155
Clavulanic acid, 2053
amoxicillin with (Augmentin), 2053
ticarcillin with (Timentin), 2053
Clear cell(s)
of sinus node, 122
Clear zone, 114
Clearance
drug, 470-471
Clearance technique(s), 450-451
injection, 452
Cleocin. *See* Clindamycin
Cleveland, M.
on situs inversus, 1284
Clindamycin (Cleocin), 2059
parenteral dosage for severe infection, 2057t
Clinical engineer(s)
role in medical instrument life cycle strategy, 544-545
Clinical nurse specialist
home visits by, 2526
Clinical trial
randomized, 145t, 147-148
Clonality
defined, 2247
Clonidine (Catapres), 2434t
hypoadrenergic dysautonomia due to, 340
use of, during pregnancy, 2386, 2387t
Cloning, 7, *8,* 23-25
cosmid, 10
defined, 61
M13, 9
methods for, 9
polymerase chain reaction in, 26, *27*
Clotting. *See* Coagulation
Cloxacillin, 2052
Clubbing, 679, *2415*
in infective endocarditis, 2422
Coagulation. *See also* Hemostasis
abnormalities of
"cardiac," 2342-2343
postoperative problems with, 2260
promotion of
by pulmonary vascular endothelium, *367,* 367
Coagulation factor(s). *See also* particular factors
isolated deficiencies of
implications for surgery, 2343-2344
Coagulation necrosis, 1693
Coagulative myocytolysis, 1693
Coanda effect, 1344
Coarctation of the aorta, 1353-1373
abdominal, 980-981, *1365,* 1366
therapy for, 1368
adult
defined, 1353
anatomy of, 1353-1354, *1354-1356*
angiographic assessment of, 958t, 1363, *1363*
anomalous right subclavian artery with, 1428, 1439
signs and symptoms of, 1431
cardiac catheterization in, 1362-1363
clinical features of
in infancy, 1363-1366
presenting past infancy, 1358-1363, *1359-1363*
collateral circulation in, *1358,* 1358
computed tomography assessment of, 883, *891-892*
defined, 1357
definition of terms in, 1353-1354
digital subtraction angiography in, *909-910*
Doppler assessment of, 793, *795*
double-outlet right ventricle with, 1223
ductal closure and, 1356, *1357,* 1357
echocardiographic findings in, 776-777, 1360-1361, *1361-1362*
in fetus, 811
in infancy, 1364
electrocardiographic findings in, 1360
in infancy, 1364, *1365*
embryology of, 1356-1357
employment and insurability and, 1373
epidemiology and genetics of, 1357
functional, 1366
infantile
defined, 1353
ischemic spinal cord injury after repair of, 1371, 2259, 2313, 2455
malformations associated with, 1354-1356
multiple sites of, 1366, 2031, *2032*
murmur of, 687
supraclavicular bruit vs., 1924
natural history of, 1366-1367
neurologic complications associated with, 1366-1367, 2311
nuclear magnetic resonance imaging in, 855-856, *856-857,* 1361, *1362*
patent ductus arteriosus with, 1060, 1067
physical examination in, *1359,* 1359-1360
physiology of, 1357-1358, *1358*
postductal, 1353
preductal, 1353
pregnancy and, 1367, 1373, 2379
renal response to, 2427
reversed, 1366
roentgenographic findings in, 703, *708-709, 1360,* 1360
in infancy, 1364
surgical treatment of, 1368-1371, *1369-1370,* 2031
complications of, 2033, 2263
decisions and techniques for, 2216, *2217*
patient selection for, 2033
postoperative followup and outcome of, 1372-1373
residua of, 2031-2033, *2032*
restenosis after, 2033, 2196-2197
sequelae of, 2033, *2033-2034*
systemic hypertension after, 1993-1994
systemic hypertension due to, 1993
therapy for, 1367-1373. *See also* Coarctation of the aorta, surgical treatment of
balloon dilation, 1371-1372, *1372,* 1964, 2196-2197, *2197-2198*
in infancy, 1364-1366, 1968
in neonatal period, 1964
medical, 1368
prostaglandin in, 1368, 2120
transposition of the great arteries with, 1178
unusual forms of, 1366
Coarctation syndrome, 1356
clinical features of, 1363-1366
Coated pits, 155
Cobb method of curve measurement, 2446, *2449*
Cobra venom factor
for myocardial protection, 270
Cocaine
cardiovascular effects of, 1671
myocardial infarction due to, 1713-1714
syncope due to, 1941
Code
defined, 546
"Code Medication" Worksheet, 2555
Codeine
dosage adjustment for renal insufficiency, 2440t
Coding region of DNA
defined, 61
Coding region of mRNA
defined, 61
Codon(s), 5-6, 6t
defined, 61
initiation, 6, 62
nonsense, 6
termination, 6
Coelom
intraembryonic, 75
Coeur en sabot, 703, *1081,* 1081
Coherence
defined, 616
Cohesive termini
defined, 61
Cohort
defined, 145
Cohort study design, 145t, 145-146
Coil(s)
embolization, 1479, 2202, *2203*
Coincidence detector, 619-620, 623
Cold pressor test, 334
Colestipol
digoxin interaction with, 2363
Collagen
in neural crest cell migration, 164
lipid deposition in, 482-483
Collagen vascular disease. *See* Connective tissue disease(s)
Collecting duct(s)
hydroosmotic response to ADH in, *455,* 455
Collimator(s)
defined, 623
for blood pool imaging, 837, *838*
for digital subtraction angiography, 636-637
for gamma cameras, 566-567, *567*
sensitivity of, 569
spatial resolution of, 569
Colony hybridization, 7, *8*
Color flow mapping. *See* Doppler echocardiography, color
Community intervention trial, 145t, 148
Compartmentation
cellular, 197-198
Complete atrioventricular canal. *See under* Atrioventricular canal defect(s)

Compliance
chest wall, 351-352
lung, 351t, *351*, 351-352
frequency dependence of, 353
ventricular
end-diastolic pressure-volume relationship and, 233
in fetus and newborn, 240
Compton scatter, *562*, 562
Computed tomography (CT)
basic science aspects of, *628-629*, 628-634
block diagram of scanner, *628*
cine-, *633*, 633-634, *882*, 882-883
cardiac chamber volume data from, 497
cine mode, 633, 883
congenital heart disease assessment with, *896*, *898-902*, 903t, 903
flow mode, 633, 882-883
volume mode, 633-634, 883
clinical aspects of, 880-904
computer applications in, 667
digital radiography in, *881*, 881
dynamic scanning method, 881
fast scanning methods, 882-883
gated, 632, 881-882
hardware configurations for, *631-632*, 631-632
image quality in, 628-630, *629-630*
imaging with, 630t, 630-631, *631*
of cardiac lesions, 897-903, *898-903*
of great vessels, 883-897, *890-896*
of mediastinal lesions, *896-897*, 897
of pericardial lesions, 883, *888-889*
in myocardial infarction diagnosis, 1710-1711
intravenous contrast with
allergic reactions to, 880-881
importance of, 883, *884-887*
injection technique, 881
motion artifacts in, 883, *888*
procedure for, 880-881
sedation for, 881
single photon emission (SPECT) myocardial imaging with, 844
Computer(s), 656-668
analog, 656
application programs for, 662-666
data input into, 658
data processing by, 658
development of, 657-658
digital, 657
electrocardiograph processing by, 516-518, *517*
for digital subtraction angiography system, 639
for statistical analysis, 647
literature search using, 644
local area networks for, 664
macro sequences for, 662
mainframe, 659
medical applications of, *657*, *666-667*, 666-667
memory of, 658-659
nomenclature of, 657
operating systems for, 660-661
output from, 659-660
plotters for, 660
printers for, 660
programming languages for, 661-662
reference programs using, 644
software for, 660-666
types of, 656-657
types of systems, 659-660
video monitors for, 659
Concordant
defined, 1280
Conductance
defined, 302-304, 502
Conduction, 299-301, *300*
age-related changes in, 309
anisotropic, 301
disease's effects on, 310
disorders of. *See also* particular disorders
blood pool imaging in assessment of, 843
intraventricular, 733-740, 1787-1796
mechanisms of arrhythmias due to, 311-313
molecular basis of, 55
exercise electrocardiography in assessment of, 1738-1739, *1739*
retrograde
evaluation of, on electrophysiology studies, 1746-1747, *1747*
sinoatrial
assessment of, on electrophysiology studies, *1766*, 1768-1772, *1769-1771*
sinoventricular
in hyperkalemia, 747
velocity of
age-related changes in, 309
determinants of, 300-301
Conduction system. *See also* particular structures
anatomy of, 121-125
development of, *103*, 104-105
distal
gating mechanism in, 1787, *1788*
isomyosins of, 218
Conduit(s)
choice of, 2212
for Rastelli operation for complex transposition, 1207-1208
for repair of tetralogy of Fallot with pulmonary atresia, *1093*, 1094
Confounding
in research studies, 150
Congenital contractural arachnodactyly, 2397
Congenital heart disease, 997-1481. *See also* particular defects
age at diagnosis of, 671
factors influencing, 1959, 1960t
air travel and, 448
altitude and, 447
atherosclerosis and, 1993
care of neonate with, 2483-2486
causation of
areas of investigation in, 137t, 137-138
theories of, 139
classification of, 1281t, 1281-1282
clinical assessment of, 671-679
computed tomography assessment of, 897-903, *898-902*, 903t
cyanotic. *See also* Cyanosis
emergency management of, 2545t
glomerular abnormalities in, 2427
hypoxic ventilatory response in, 442
developmental considerations for child with, 2521-2522
diagnosis of
nondefinitive vs. potentially definitive modalities in, 1960-1961, 1961t
segmental approach to, 769
digital subtraction angiography in assessment of, 908, *909-910*
echocardiographic diagnosis of, 769-780, *778-780*
effects on education, 2524-2525
epidemiology of, 135-141
causation in, 137t, 137-139
conceptual issues, 135-136
enumeration and estimation in, 136-137
intervention in, 139t-140t, 139-141
projection in, 141
extracardiac malformations with, 677t-678t, 677-679
fetal pulmonary circulation in, 364
frequency of occurrence of, 136-137
growth failure in, 2355-2356
in first year of life, 1959-1972
mode of presentation of, *1961*
presenting at 0-3 days, 1960t, 1960-1963
presenting at 4-14 days, 1963t, 1963-1965
presenting at 2-18 weeks, 1965t, 1965-1967
presenting at 4-12 months, 1967t, 1967-1969
with unpredictable age of presentation, 1968-1969
infective endocarditis and, 1561-1562
morphology of pulmonary vascular disease with, 371-372
natural history of
epidemiologic studies of, 137
neurologic complications of, 2305-2315
orthopedic management of, 2453-2455
noncardiovascular surgery in
anesthesia maintenance for, 2298-2299
orthopedic sequelae of complications in, 2451-2456
parental reactions to
after birth, 2520-2521
during pregnancy, 2519-2520
physical examination in assessment of, 679-683
physiologic prototypes of, 999
plain radiographic diagnosis of, 691-712
pregnancy in, 2378-2380
prevention of
approaches to, 139t, 139-140
pulmonary elasticity in, 350
renal malformations with, 2428, 2429t-2430t
scoliosis in, 2449-2451
siblings' reactions to, 2522-2523
supraventricular tachycardia and, 1811-1812
surgical treatment of
congestive heart failure after, 2014-2015
decisions and techniques in, 2210-2226
history of, 2289-2290, 2290t
residua, sequelae and complications of, 2024-2043
sites of right bundle branch block after, 1788
ventricular arrhythmias after, 1894-1896, 2181
survival into adulthood with
epidemiologic studies of, 141
teratogens and, 676t, 676
unoperated
congestive heart failure in, 2014
ventricular arrhythmias with, 1891-1892
Congenital phlebectasia, *2423*, 2423
Congenital rubella syndrome. *See* Rubella, congenital
Congestive cardiomyopathy. *See* Dilated cardiomyopathy
Congestive heart failure, 2007-2023
abnormal autonomic/cardiovascular interaction in, 245-246, 340-341
atrial septal defect with
effects of repair on, 1035-1036
cardiac catheterization in, 2010
chronic
chronic liver disease vs., 2361-2362
liver findings in, 2361
response to inotropic agents and, 2073-2074
clinical recognition of, 2007-2010
compensatory mechanisms in, 244-247

in developing heart, 245
contraceptive choice and, 2372
depressed contractility in
cellular mechanisms of, 247-248, *248*
echocardiographic findings in, 2010
etiology of, 2010-2015
presenting in childhood and adolescence, 2013-2015, 2014t
presenting in fetus, 2010-2011
presenting in infancy, 2011t, 2011-2013
euphemisms for, 2020
hematologic complications of, 2343
in acquired heart disease, 2015
in congenital heart disease, 673
postoperative, 2014-2015
preoperative, 2014
in fetus. *See also* Hydrops fetalis
etiology of, 2010-2011
management of, 2011
laboratory findings in, 2009-2010
management of, 2015-2020
diet in, 2020
emergency, 2544t
mechanisms of, 244-249
patent ductus arteriosus with, 1062
patient history in, 2008
physical examination in, 2008-2009
pleural effusion with, 2514
radiologic findings in, 2009
radionuclide studies in, 2010
renal response to, 244-245, 340, 2425-2427
serum bilirubin in, 2361
supraventricular tachycardia and, 1812t, 1812-1813
sweating and, 1007-1008
Connective tissue disease(s). *See also* Autoimmune disease; particular diseases
cardiovascular manifestations of, 1527-1541
electrocardiographic findings in, 754
hematologic and oncologic problems with, 2330
maternal
congenital complete atrioventricular block and, 1803, 1908
molecular basis of, 47-49
steroid therapy for, 2497
Connective tissue matrix component(s)
pulmonary vascular endothelial cell synthesis of, 366
Conotruncal septum. *See* Ventricular septum, outlet
Conoventricular flange, 81
Conoventricular foramen, 81
Conoventricular ledge, 81
Consensus sequence
defined, 61
Constrictive pericarditis. *See under* Pericarditis
Continuity equation
valve area estimation using, *799*, 799
Continuous arteriovenous hemofiltration, 2438t-2439t, 2438-2439
Continuous positive airway pressure (CPAP)
for persistent pulmonary hypertension in neonate, 2485
in postoperative care, 2254
Contraception, 2371-2373. *See also* Contraceptive(s)
counseling patients about, 2526
Contraceptive(s). *See also* Contraception
oral, 2373
effects on pulmonary circulation, 379
myocardial infarction due to, 1714
Contractile apparatus
elements of, 32-40
Contractile protein(s), 212-222. *See also* particular proteins
enzymatic activity of, 217
isoforms of, 217-220
Contractility, 236, *237*
basal
indices of, 226-227, *227*, 228
changes in
in cardiac hypertrophy, 36, 246
in congestive heart failure, 245-246, 247-248, *248*
in ischemia, 267
clinical physiology of obstructive and regurgitant lesions and, 1307
defined, 223
heart rate and, *229*, 230
in fetus and newborn, 240-241
indices of, 223-230
based on end-systolic pressure-volume relationship, 227-228, *228-229*
ejection phase, 226-227
preejection phase, 225-226
myocardial oxygen consumption and, 252
stroke volume and, 238-239, *239*
Contraction, 202-222, 2065-2067, *2066-2067*
abnormal patterns of, 1694
atrial
ventricular preload and, 233
molecular organization of
in striated muscle, *212*, 212
theories of, 214-215
Contraction band necrosis, 1693
Contraction stress test, 2391-2392, 2392t
Contrast agent(s)
for angiocardiography, 952t, 952-954
cardiovascular effects of, 952-953
dose of, 953t, 953-954
priorities in injection of, 954
toxic reactions to, 953
for computed tomography
allergic reactions to, 880-881
importance of, 883, *884-887*
injection technique, 881
for echocardiography, 780
for peripheral vascular angiography, 974, 975t
adverse effects of, 975
low-osmolarity, 974, 975t, 994
reduced dosage of, in digital subtraction angiography, 908, 911
Contrast resolution
x-ray system evaluation using, 629
Contrast-to-noise ratio
in nuclear magnetic resonance, 867-868, *868*
Contusion
cardiac, 2535-2536
Conus, 81
Conus artery(-ies)
left, 1453
right, 125, 1454
Conus ligament, 111
Cooley's anemia. *See* Thalassemia(s)
Cooling. *See also* Hypothermia
in supraventricular tachycardia management, 1823
Coombs, Carey F., 688t
Copper
cardiac function and, 2363
Cor pulmonale, 2501-2506
acute, 2501
causes of, 2503t, 2503-2504
diagnosis of, 2502-2503
electrocardiographic findings in myocardial infarction vs., 1715
prognosis in, 2506
therapy of, 2504-2505
Cor triatriatum, 1308-1309
pulmonary venous disease secondary to intrapulmonary veno-occlusive disease vs., 2510
radiographic findings in, 703-707, *710*
rheumatic mitral stenosis vs., 1511
Corgard. *See* Nadolol
Cori disease, 1665
Cornelia de Lange's syndrome, 678t, 679, *2410*, 2410-2411
Coronary angiography. *See under* Angiography
Coronary angioplasty
percutaneous transluminal. *See under* Balloon angioplasty
Coronary arteriography. *See under* Angiography
Coronary arteriosclerosis. *See* Coronary artery disease
Coronary arteritis
coxsackie B
myocardial infarction in, 1713
in Kawasaki disease, *1547-1549*, 1552-1554, *1553-1554*
in rheumatic fever, 1491
Coronary artery(-ies)
abnormalities of
chest pain due to, 1949
myocardial infarction due to, 1686
anatomy of, 125, 1453-1454, *1454*
minor variations of, 1454
aneurysm of
in Kawasaki disease, 1546, *1547-1549*, 1552-1554, *1553-1554*, *1558*
anomalies of. *See* Anomalous coronary artery(-ies)
delimiting
in double-inlet left ventricle, 1252-1253, *1253*, 1459-1460, *1460*
development of, *102*, 103-104
dominant left system of, 1453
dominant right system of, 1454
echocardiographic assessment of, 775-776
histologic features of, *122*, 126, *127*
in transposition of the great arteries, 971, 1176-1177
in ventricular inversion, 1240-1241
intramural, 126
left
anomalous. *See under* Anomalous coronary artery(-ies)
normal anatomy of, 1453-1454, *1454*
left anterior descending, 125, 1453-1454
blood flow pattern in, *255*, 255
left atrial circumflex, 1453
left circumflex, 125, 1453
minor variations of, 1454
left main, 125
medial necrosis of
endocardial fibroelastosis vs., 1626
patterns of, associated with congenital heart defects, 1458-1460
posterior descending, 1453, 1454
right, 125, *1454*, 1454
anomalous. *See under* Anomalous coronary artery(-ies)
blood flow patterns in, *254*, 254-255
single. *See under* Anomalous coronary artery(-ies)

Coronary artery(-ies) *(cont.)*
small
abnormalities of, in hypertrophic cardiomyopathy, 1629
trauma to
blunt, 2537
penetrating, 2538
Coronary artery bypass grafting, 2284
for Kawasaki disease, 1558
history of, 2280
Coronary artery disease. *See also* Atherosclerosis; Myocardial ischemia
accelerated
after cardiac transplantation, 1993, 2237, 2280
acquired, 2277-2288
history of, 2277-2280
natural history of, 2278
after arterial switch procedure, 2041
clinical manifestations of, 2281-2284
diagnostic tests for, 2284
etiology of, 2280-2281
in systemic lupus erythematosus, 1531-1532
management of, 2284-2285
history of, 2279-2280
pregnancy with, 2383
premature
inborn errors of metabolism predisposing to, 47, 48t
risk factors for, 2281
Coronary artery fistula, *1460,* 1460-1461
coronary steal phenomenon with, 2281
patent ductus arteriosus vs., 1066, 1460
Coronary blood flow. *See* Myocardial blood flow
Coronary sinus
anomalies of, 1465-1467
development of, 100
unroofed, 1025, 1465, *1467*
treatment of, 1469
Coronary steal phenomenon
with anomalous left coronary artery, 1455, 1456
with coronary artery fistula, 2281
Coronary vascular reserve, *260-262,* 260-263
Coronary vein(s)
anatomy of, 126
histologic features of, 126
intramural, 126
Corrigan's pulse. *See under* Pulse
Corticosteroid(s). *See* Steroid(s); particular drugs
Corticotropin (ACTH)
increased production of, 2495
Cortisol
normal secretion of, 2496
Cortisone acetate, 2497t
Corynebacterium spp. *See also* Diphtheria
endocarditis due to, 1570
Cosmid vector(s)
defined, 61
Costochondritis, 1948
Coulomb's law, 502
Coumadin. *See* Warfarin
Coumarin, 2080-2081. *See also* Dicumarol; Phenprocoumon; Warfarin
use during pregnancy, 2080
Counseling
for parents of fetus with congenital heart disease, 2520
genetic, 172-173, 173t. *See also* particular disorders
on employment and insurance, 2532-2533
on pregnancy risk, 2383t, 2383-2384
on sexual matters, 2371-2372
Count(s)
defined, 623
Count rate
defined, 623
Countercurrent exchange system
in urine concentration, 455
Countercurrent multiplier system
in urine concentration, 454-455, *455*
Countershock, 2167-2171. *See also* Cardioversion; Defibrillation
complications of, 2169t, 2169-2170
theories of operation of, 2167-2168
Couplet(s), 1872-1874, *1874-1875,* 1956, *1957*
acute management of, 1897
atrial
in fetus, 1907
Coupling interval
of premature ventricular contractions, *1871-1872,* 1871-1872
Coxiella burnetti
infective endocarditis due to, 1570-1571
Coxsackievirus. *See also* Coxsackievirus B
maternal infection with
congenital heart disease and, 676
Coxsackievirus B
congenital infection with, 676, 2472
coronary arteritis due to
myocardial infarction in, 1713
myocarditis due to, 1578-1579
criteria for diagnosis of, 1585
in infants, 676, 2472
molecular techniques in diagnosis of, 57
CpG dinucleotide
mutations in, 17
CPU (central processing unit), 658
for digital subtraction angiography system, 639
Creatine kinase (CK), 55-56
assay of
in myocardial infarction diagnosis, 1685, *1698,* 1698
Creatinine clearance
estimation of, 452t, *452,* 452
Cri du chat syndrome, 184, 678t, 2429t
Crick, Francis, 4-5
"Crisscross" heart, *1240,* 1240
Crista supraventricularis, 115-116, 1003
Crista terminalis, 113
Critical closing pressure, 431
Critical pressure, 431
Crohn's disease
ankylosing spondylitis and, 1536
pharmacokinetics of beta blockers in, 2365
Cross talk
defined, 2153
Cross-bridge(s), 213. *See also* Actomyosin complex
in sliding filament theory of contraction, 214, *216,* 216-217, 2065-2066, *2066*
Crossing over, *14,* 14, 177
defined, 61
Crossover design
in randomized clinical trial, 148
Cross-sectional study design, 144-145, 145t
Crowe's sign, *2416,* 2416
Crux cordis, 111
Crystal
in positron emission tomography
defined, 623
Crystalloid
pump oxygenator priming with, 2300
CT number, 630
for biologic tissues, 630t
Culture(s)
in brain abscess diagnosis, 2047, 2309
in infective endocarditis diagnosis, 1564-1565, 2047-2048
skin fibroblast
for chromosome analysis, 178
techniques for, 2047-2048
Current
defined, 2140
Cushing's syndrome, 2495
due to steroid therapy, 2497
Cutis laxa
autosomal recessive, 49
X-linked recessive, 2404t
Cutis marmorata, 672
Cutis marmorata telangiectatica congenita, *2423,* 2423
Cyanide toxicity
with nitroprusside, 2088
Cyanosis, 671-672
central, 672
determinants of degree of
in right-to-left shunt, 1070-1072
differential, 672
in coarctation of the aorta, 1364
in patent ductus arteriosus with right-to-left shunt, 1060, 1061
hemoglobin level and, 1072
in tetralogy of Fallot, 1080
Cycle (ultrasound)
defined, 526
Cyclic adenosine monophosphate (cAMP)
isomyosin activity regulation by, 220
synthesis of
beta-adrenergic receptors in, 321
enzymatic control of, 321-322, *322*
Cyclophosphamide
cardiotoxicity of, 1673, 2341, 2342
doxorubicin cardiotoxicity and, 2339
Cyclopropane
effects on electrocardiogram, 751
Cyclosporine
cutaneous reactions to, 2422, *2423*
drug interactions with, 2235
for immunosuppression after heart transplantation, 2235t, 2235, 2243
in rejection treatment, 2236
lymphoma and, 2247
molecular events of immunosuppression by, 2243
neurologic complications of, 2314-2315
posttransplant infection and, 2245, 2246t
trimethoprim-sulfamethoxazole interaction with, 2060
Cyst(s)
aneurysmal bone
embolization for, 992
blood. *See* Blood cyst(s)
pericardial
computed tomography assessment of, *889*
Cystic fibrosis
altitude and, 447-448
congestive heart failure due to, 2015
cor pulmonale in
diagnosis of, 2502-2503
mechanism of, 2503
prognosis in, 2506
supplemental oxygen in, 2505
Cystic hygroma
computed tomography assessment of, *887*
Cytidine monophosphate (CMP), 14
Cytochrome C oxidase deficiency, 1668
Cytogenetics, 175-178
Cytomegalovirus infection

after heart transplantation, 2245, 2467-2468
congenital
cutaneous manifestations of, *2421*, 2421
in acquired immune deficiency syndrome, 1609
maternal
congenital heart disease and, 676
postperfusion syndrome and, 1603, 2342
Cytoplasmic segregation, 158, *159*
Cytotrophoblast, 72

D600
mechanism of action of, 305
Da Vinci, Leonardo
on atherosclerosis, 1989
on heart, 1453
Dacarbazine
doxorubicin cardiotoxicity and, 2339
Damadian, R., 570-571
Damus-Kaye-Stansel operation, 2217, 2220
Dantrolene, 2554t
Data
comparing groups of, 649-651
three or more, 651-652
computer processing of, 658
distribution of, 648-649
input of, into computer, 658
nonparametric
analysis of, 652-653
paired, 650
Database(s)
computer programs for, 662-663, *663*
Daunorubicin (daunomycin)
cardiotoxicity of, 1672-1673, 2339-2340
De Lange's syndrome, 678t, 679, *2410*, 2410-2411
De Musset's sign, 1515
Dead space
alveolar, 356
anatomic, 356, 432
functional, 432
physiologic, 356, 432
Dead time
in nuclear cardiology, 567
in positron emission tomography, 623
Death
patients' attitudes toward, 2526
Debrancher enzyme deficiency
in Cori disease, 1665
Decoupling
in nuclear magnetic resonance spectroscopy, 611
Defense reaction, 327
Deferoxamine
iron chelation therapy with
in thalassemia management, 2333-2334
Defibrillation, 420-421, 2167
complications of, 2169-2170
determinants of threshold of, 2168t, 2168-2169
dosage for, 421, 2168, 2171
for pacemaker patient, 2170
specifications for, 421
theories of operation of, 2167-2168
Defibrillator
implantable
for long Q-T syndrome, 1890
for ventricular arrhythmias, 1900
Degeneracy
defined, 61
Degrees of freedom, 649
in analysis of variance, 652
Deletion(s)
chromosomal, 177
Delimiting artery(-ies)
in double-inlet left ventricle, 1252-1253, *1253*, 1459-1460, *1460*
Delivery. *See* Labor and delivery
Delta wave
in Wolff-Parkinson-White syndrome, *739*, 739
Demerol. *See* Meperidine
Dental abscess(es), *2352*, 2352
Dental disease
assessment for, 2352-2353, *2353*
in congenital heart disease patients, 2351
prevention of, 2351-2352
Dental procedure(s)
bacteremias related to
incidence of, 2350-2351, 2351t
endocarditis and, 676, 2351
invasive
precautions for, 2352
Dentistry, 2350-2353
Deoxyadenosine monophosphate (dAMP), 4
Deoxycytidine monophosphate (dCMP), 4
Deoxyguanosine monophosphate (dGMP), 4
Deoxyhemoglobin
selective T2 relaxation due to
in nuclear magnetic resonance, 604
Deoxyribonuclease(s) (DNase)
sensitivity to
gene activation and, 17
streptococcal production of, 1487
Deoxyribonucleic acid (DNA)
analysis of, 20-21
cloning of. *See* Cloning
coding region of
defined, 61
complementary (cDNA)
defined, 61
synthesis of, 23
defined, 61
discovery of, 3
double-stranded
structure of, 11
ends of fragments of
defined, 61
eukaryotic, 11-12
genomic
defined, 62
isolation of, 23
labeling methods for, 21
libraries of, 10
linker, 15
methylation of
gene activation and, 17
polymorphisms
defined, 61
primer
defined, 61
regulatory sequences of, 17-18
repetitive sequences in, 15
replication of, 5
in eukaryotes, 12, *13*
semiconservative, 12
selfish, 15
sequencing of
methods for, 9, *10-11*, 23
polymerase chain reaction in, 26-27, *27*
structure of, *4-5*, 4-5
Deoxyribonucleic acid ligase, 7
Deoxythymidine monophosphate (dTMP), 4
Depo-Provera
intramuscular, 2373
Depth-resolved surface coil spectroscopy (DRESS), *613*, 613
Desktop publishing, 662
Determination, 158
Dexamethasone, 2497t, 2554t
Dextran
antiplatelet therapy with, 2081
streptococcal production of
infective endocarditis and, 1562
Dextrocardia, 1282-1285
cardiac abnormalities associated with, 1283-1285, 1284t
clinical evaluation of, *1283*, 1283
defined, 725, 1280
diagnosis of
in fetus, 807
embryology of, 1282
incidence, genetics and etiology of, 1282
mirror-image, *725*
defined, 1283
electrocardiographic findings in, 725-726, *726-727*
mixed
defined, 1283
nomenclature and classification of, 1282-1283, 1283t
pivotal
defined, 1283
secondary, 1283
ventricular inversion with, 1239
with situs inversus, 1287
cardiac abnormalities associated with, 1284t, 1284-1285, *1286*
with situs solitus
cardiac abnormalities associated with, 1283-1284, *1284*, 1284t
Dextro-looping. *See* Cardiac looping
Dextroposition
defined, 1283
Dextrorotation, *725*. *See also* Dextrocardia
defined, 1283
electrocardiographic findings in, *726*, 726
Dextrose, 2553t
Dextroversion. *See also* Dextrocardia
defined, 1283
Diabetes mellitus, 2495-2496
antibiotic absorption in, 2049
atherosclerosis and, 1992
cardiac protein synthesis and degradation in, 199
hypoadrenergic dysautonomia due to, 339
in fetal rubella syndrome, 2499
isomyosin changes in, 37, 219
maternal
congenital heart disease and, 676t, 676
endocrine abnormalities in child in, 2498t, 2499
Diabetic ketoacidosis
management of, 2495
Diacylglycerol (DAG), 320
Diagnosis
invasive methods for, 905-996
molecular techniques in, 20-30
noninvasive methods for, 669-904
prenatal
cytogenetic techniques for, 178
molecular techniques in, 20
psychological impact of, 2519-2520
value of, 173
Dialysis. *See also* Hemodialysis; Peritoneal dialysis
choice of method of, 2437-2438, 2438t

Dialysis *(cont.)*
indications for, 2437t, 2437-2438
pericarditis and, 2432-2433
Diamagnetism, *603,* 603, 616
effects on nuclear magnetic resonance images, 604
Diaphorase I
in methemoglobin reduction, 2335
Diaphragm
efficiency of
work of breathing and, 355
in ventilation, 354
irritation of
chest pain due to, 1948
paralysis of, 2511-2512
Diastolic depolarization. *See* Automaticity
Diastolic flow period, 943
Diastolic flow time, 943
Diastolic pressure half-time
echocardiographic estimation of mitral stenosis severity by, 1509
Diastolic pressure-time index (DPTI)
subendocardial blood flow estimation from, 261, 1336
Diastolic rumble
innocent fourth heart sound vs., 1925
innocent third heart sound vs., 1925
Diazepam (Valium), 2553t
dosage adjustment for renal insufficiency, 2440t
for obstetric analgesia, 2387t, 2389
hemodynamic effects of, 2294t
premedication with
for cardiac catheterization, 948
Diazoxide (Hyperstat), 2549t
effects on pulmonary circulation, 374t, 377
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2367
Dichloroacetate
for metabolic acidosis with cardiac arrest, 417
Dicloxacillin, 2052
Dicumarol, 2553t
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2367
Dideoxy method, 9, *11*
Diet. *See also* Nutrition
after cardiac transplantation, 2234
cholesterol and, 479
in congestive heart failure management, 2020
in preventive dental program, 2351-2352
patients' attitudes toward, 2526
sources of hydrogen ions from, 460t, 460
Diethyl ether
electrocardiogram and, 751
Diethylenetriamine pentaacetic acid (DTPA)
technetium-labeled, 564
Differentiation
defined, 158
Diffusible tracer(s)
blood flow measurement using, 256, 495, 622
Diffusion
pulmonary, 355-356
altitude's effects on, 442
measurement of, during exercise, 833
tissue
altitude's effects on, 443
DiGeorge syndrome, 1376, 2409
cardiac and renal anomalies in, 2430t
endocrine abnormalities in, 2498t, 2498-2499
hematologic and oncologic problems with, 2329t, 2330
monosomy 22q11 and, 187
neural crest injury and, 162
truncus arteriosus in, 1129
Digital scan converter
echocardiogram signal processing by, 530
Digital subtraction angiography (DSA), 973
basic science aspects of, 635-641
cardiac applications of, 907-908
clinical aspects of, 907-912
components of system for, 636-639, *637*
conventional imaging vs., 908-911, 973
dynamic range correction in, 637-638
future directions in, 911
history of, 635-636
image acquisition in, 639-640
image processor features and function in, 639-641
image storage in, 640-641
intra-arterial, 973
intravenous, 973
mask-mode, 907
minimizing patient motion in, 638, 908
technique of, 908
time interval-difference, 907
Digitalis
atrial flutter induced by, 1853
cardioversion in patient taking, 1857
effects on electrocardiogram, 749-750, *750*
hypercalcemia's interaction with, 748
hypokalemia's interaction with, 747
in atrial flutter treatment, 1855-1856
in congestive heart failure management, 2017
in cor pulmonale management, 2505
in idiopathic dilated cardiomyopathy management, 1622-1623
in mitral stenosis management
in pregnancy, 2378
in myocarditis management, 1586
in patent ductus arteriosus management, 2487-2488
intestinal ischemia and, 2359
problems with
in Wolff-Parkinson-White syndrome, 1914
toxicity of
digoxin-specific antibody fragments in management of, 2133
effects on electrocardiogram, 749-750, *750*
use of countershock in, 2169-2170
use of, in pregnancy, 2384, 2385t
ventricular arrhythmias due to
treatment of, 1897
Digital-to-analog converter
defined, 616
Digitoxin, 2127t, 2128
dosage adjustment for renal insufficiency, 2441t
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2363-2364
Digoxin, 2127t, 2127-2128, 2552t
clinical use of, 2071-2072
dosage adjustment for renal insufficiency, 2441t
drug interactions with, 2052, 2072, 2128, 2363
for atrial fibrillation
problems with, in Wolff-Parkinson-White syndrome, 1860-1861
for congestive heart failure, 2017, 2017t
for fetal tachycardia, 1908-1910
in supraventricular tachycardia management, 1823-1824
in ventricular septal defect management, 1015
inactivation of, by intestinal bacteria, 2363
indomethacin interaction with, 2118
monitoring of, 2017
pharmacology of, 2071, 2127, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2363
radioimmunoassay for
spironolactone interference with, 2106
toxicity of, 2127-2128
diagnosis of, 2072
treatment of, 2072
use of, in pregnancy, 2384
verapamil interaction with, 2072, 2128, 2133
Digoxin-like immunoreactive substance(s)
in liver disease, 2363
in newborn, 2071
Digoxin-specific antibody fragments, 2133
Dihydroergotamine
effects on pulmonary circulation, 374t, 377-378
Dilantin. *See* Phenytoin
Dilated cardiomyopathy, 1618-1626. *See also* Endocardial fibroelastosis
characteristics of, 1617, 1619t
congestive heart failure due to, 2013
pathophysiology of, 1620
idiopathic, 1619-1624
clinical picture and laboratory findings in, 1620-1621, *1621-1623*
etiology of, 1619
hemodynamics and angiography in, 1621-1622
pathology of, 1619-1620, *1620*
pathophysiology of heart failure in, 1620
prognosis in, 1624
treatment of, 1622-1624
molecular basis of, 54
nuclear magnetic resonance imaging in, 864, *865*
presenting in infancy, 1968-1969
vasodilators for, 2091-2093, *2092*
ventricular arrhythmias in, 1893
Dilation
balloon. *See* Balloon angioplasty; Balloon valvuloplasty
cardiac
in compensation of congestive heart failure, 244-245
Diltiazem
dosage adjustment for renal insufficiency, 2440t
effects on pulmonary circulation, 374t, 378-379
for myocardial protection, 271
hepatic and renal toxicity due to, 2368
mechanism of action of, 305
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2366
Dimethylthiourea
effects on postischemic dysfunction, 274-275
Diphenhydramine (Benadryl), 2554t
Diphenylhydantoin. *See* Phenytoin
Diphosphopyridine nucleotidase, 1487
Diphtheria
cardiac manifestations of, 2468-2469
endocarditis due to, 1570
myocarditis due to, 1581
Diploidy
defined, 12, 175
Dipole
heart as, 500-502, *501-502*
Dipyridamole (Persantine), 2553t
antiplatelet therapy with, 2081
as stress inducer
for myocardial perfusion imaging, 844, 1710
dosage adjustment for renal insufficiency, 2441t

in pulmonary vascular disease management, 2003
Disability insurance, 2529-2530
Discoid rash
in systemic lupus erythematosus, 1529
Discordant
defined, 1280
Disintegration
defined, 623
Disintegration rate
defined, 623
Disk drive(s), 658-659
types of, 640
Disopyramide, 2127t, 2129, 2550t
congestive heart failure due to, 675
dosage adjustment for renal insufficiency, 2441t
effects on electrocardiogram, 750-751
for ventricular arrhythmias, 1898
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2365
use of, during pregnancy, 2385-2386, 2386t
Dispermy, 176
Disseminated intravascular coagulation, 2344
Distribution of data, 648-649
Diuretic(s), 2099-2107, 2548t. *See also* particular drugs
dosage for, 2102t
adjustment for renal insufficiency, 2441t
in congestive heart failure management, 2016-2017
in cor pulmonale management, 2505
in myocarditis management, 1586
in patent ductus arteriosus management, 2488
in persistent pulmonary hypertension management in neonate, 2485
in pulmonary disease treatment
cardiac effects of, 2506
in renal failure prevention, 2436
in ventricular septal defect management, 1015
loop, 2100-2103
complications of, 2102-2103
drug interactions with, 2103
in congestive heart failure management, 2016
indications for, 2102
pharmacokinetics of, 2102
pharmacology of, in hepatic, gastrointestinal or nutritional disorders, 2366
use of, during pregnancy, 2387t
mechanisms of action of, *2101*
mercurial, 2106
osmotic, 2106
pharmacology of, 2099-2100
in hepatic, gastrointestinal or nutritional disorders, 2366
potassium-sparing, 2105-2106
thiazide, 2103-2105
complications of, 2105
cutaneous reactions to, *2422*, 2422
in congestive heart failure management, 2016
indications for, 2104-2105
mechanisms of action of, 2103-2104
nonrenal effects of, 2104
pharmacokinetics of, 2104
pharmacology of, in hepatic, gastrointestinal or nutritional disorders, 2366
use of, during pregnancy, 2386, 2387t
use of, during pregnancy, 2386, 2387t
Diuril. *See* Chlorothiazide
Diverticulum(-a)
ductus
acute aortic injury vs., 978
Kommerell's. *See* Kommerell's diverticulum
Diving reflex, 335
in supraventricular tachycardia treatment, 1821
in syncope diagnosis, 1945
Dizziness
sudden death and, 675
D-looping. *See* Cardiac looping
DNA. *See* Deoxyribonucleic acid
DNase. *See* Deoxyribonuclease(s)
Dobutamine, 2070-2071, 2548t
as stress inducer
for myocardial perfusion imaging, 844
effects on pulmonary circulation, 374t, 375
in cardiopulmonary resuscitation, 420
in congestive heart failure management, 2018t, 2018
in myocardial infarction management, 1717
in myocarditis management, 1586
in postoperative management, 2257
mechanisms of action of, 2068t
pharmacology of, 2070-2071
in hepatic, gastrointestinal or nutritional disorders, 2364
use of, in pregnancy, 2385t
Dominant inheritance
defined, 61
L-Dopa
hypoadrenergic dysautonomia due to, 340
Dopamine, 2070, 2548t
analogues of, 2068
dobutamine with, 2071
effects of
on pulmonary circulation, 374t, 375
on renal blood flow, 451
in cardiopulmonary resuscitation, 420
in congenital heart disease management in neonate, 1961
in congestive heart failure management, 2018t, 2018
in myocardial infarction management, 1717
in myocarditis management, 1586
in persistent pulmonary hypertension management in neonate, 2485, 2486
in postoperative management, 2257
in renal failure prevention, 2435-2436
in renal response to congestive heart failure, 2426
mechanisms of action of, 2068t, 2073
nitroprusside with
for heart failure after cardiac surgery, 2095
pharmacology of, 2070
in hepatic, gastrointestinal or nutritional disorders, 2364
use of, in pregnancy, 2385t, 2385
Dopamine receptor(s), 328, 2068, 2426
Doppler echocardiography, 784-804
angle of incidence in, *535*, 535
basic science aspects of, 534-541
blood flow measurement by, 497-498, 793-796
clinical validation of, 795-800
color, 532, 539-540
equipment for, 785
of fetus, 823-825
uses for, 787
ventricular septal defect assessment by, 1011
continuous wave
fetal cardiac function assessment by, 820-823, *822*, *824*
instrumentation for, 538, *539*
safety of, 540
uses for, 787
disturbed flow patterns in, 786, *787*
duplex systems for, 538
during exercise testing, 832-833
examination with
approach to, 786-787
goals of, 784, 787
procedure for, 788-793
high pulse repetition frequency, 538, *539*
in segmental assessment of cardiovascular anatomy, 769
instrumentation for, 538-539, 784-786, *785*
for fetal examination, 806
output from, 785
myocardial oxygen consumption estimation from, 253
normal flow patterns in, 786
of fetus
cardiac function assessment by, 820-823, *821-825*
heart rate and rhythm evaluation with, 814-818, *814-819*
instrumentation for, 806
risks and benefits of, 825-826
peak velocity estimates with, 798-799
pressure gradient estimation by, 796-799, *798*
pulsed
fetal cardiac function assessment by, 820-823, *821*, *823-825*
instrumentation for, 538
of fetus, indications for, 820
range gating in, 538, *539*
safety of, 540
uses for, 787
quantitative methods of, 793-800
safety of, 540-541
for fetus, 825-826
shunt quantitation by, 795-796
signal processing in, 538-539, 785-786
spectral broadening in, 786
systemic venous flow assessment by, *788*, 788
ventricular septal defect assessment using, 1011
Doppler effect, 534-535, *535*
Doppler technique(s). *See also* Doppler echocardiography; Doppler ultrasound
laser
blood flow measurement using, 497
Doppler ultrasound. *See also* Doppler echocardiography
blood pressure measurement by, 681
physics of, 534-536
safety of, 540-541
Double-blind study design, 147
Double-inlet left ventricle. *See* Single ventricle
Double-outlet both ventricles, 1216
Double-outlet left ventricle, 1230
defined, 1213
Double-outlet right ventricle
anatomic considerations in, *1214-1217*, 1214-1217
cardiac anomalies associated with, 1222-1226, 1225t
cardiac catheterization and angiography in, *1215*, 1222, *1223-1224*
clinical presentation of, *1218*, 1218-1219
complex anatomy associated with, 1226-1227, *1228*
conduction system in, 1226
coronary artery anomalies with, 971, 1223-1226, *1227*, 1460
corrective surgery for, 1227-1229, *1230*
decisions and techniques for, 2220
patient status after, 1229-1230
defined, 1213

Double-outlet right ventricle *(cont.)*
echocardiographic findings in, *772,* 772, 1220-1222, *1221*
electrocardiographic features of, 1219-1220
embryology of, 162-163, 1217
great artery relations in, *1214-1216,* 1214-1216
management of, 1967
natural history of, 1227
neural crest injury and, 162-163
oxygenation in, 1218
physiology of, 1217-1218
radiographic features of, 1219, *1220*
tetralogy of Fallot vs., 1077
ventricular septal defect in, 1216-1217
Double-outlet ventricle(s), 1213-1232. *See also* Double-outlet right ventricle
left, 1213, 1230
Down syndrome (trisomy 21), 179-181
anomalous right subclavian artery in, 1428
atrioventricular canal defect and, 1041
chest radiographic findings in, 694
chromosome findings in, 180-181, *181*
clinical findings in, 179-180, *180*
congenital heart disease in, 180, 677t-678t, 677-678, 2429t
endocrine abnormalities in, 2498t, 2498
gastrointestinal problems in, 2358
hematologic and oncologic problems in, 2328, 2329t
maternal age and, 179, 180t
molecular basis of, 54-55
mosaic, 181
myeloproliferative syndrome with, 2328, *2329*
orthopedic problems in, 2456
pulmonary findings in, 2511
pulmonary hypertension in, 2000
renal anomalies in, 2429t
Doxorubicin (Adriamycin)
cardiotoxicity of, 675, 1672-1673, 2338-2339, *2340*
blood pool imaging in assessment of, 843
computed tomography assessment of, *897,* 897
dP/dt
as contractility index, *225,* 225
measurement of, 226
DR-antigen(s), 2240
Dressler's syndrome, 1600
Drop attack(s), 1940
Drug(s), 2548t-2554t. *See also* particular drugs and classes of drugs
absorption of, 471-472
interactions involving, 473-474
accumulation of, 471-472
cardiovascular
use of, in pregnancy, 2384-2387, 2385t-2387t
clearance of, 470-471
"code medication" worksheet, 2555
compliance with regimen, by adolescent patients, 2526
cutaneous complications of, 2422
distribution of, *469,* 469
developmental considerations, 470
dysautonomias due to, 340
effects on electrocardiogram, 749-752
efficacy of, 319
elimination of, 469t, 469
first-pass, 471
for cardiopulmonary resuscitation. *See under* Cardiopulmonary resuscitation
half-life of, 469t, 469
hepatic metabolism of, 470
interactions involving, 474
illegal
use of, by heart disease patients, 2526
interactions of, 473-474
mechanisms for, 473t, 473-474
intravenous infusion of, 472
lupus-activating, 1532-1533, 1533t
metabolites of
accumulation of, in renal failure, 471
clinical importance of, 473
confounding results of plasma-level monitoring, 473
modifications of therapy with
in renal insufficiency, 2439, 2440t-2441t
monitoring of, 472-473
pharmacokinetics of, 2364t
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2363-2368
protein-binding of
developmental considerations in, 470
renal excretion of, 470-471
interactions involving, 474
steady-state serum concentration of
calculation of, 471-472
with intravenous infusion, 472
syncope due to, 1941
toxicity of
age and, 2048
Drug abuse
intravenous
infective endocarditis and, 1564, 1569
Duchenne muscular dystrophy, 1675-1676, *1676,* 2317-2318, 2407
congestive heart failure due to, 2015
electrocardiographic findings in, 752
gene therapy for, 59
molecular basis of, *49,* 49-52, *51-53*
orthopedic problems in, 2458-2459
positron emission tomography studies in, 876
prenatal diagnosis of
multiplex polymerase chain reaction method in, 26
Ductus arteriosus, 117, 283
absence of
absent pulmonary valve syndrome and, 1102
agents affecting, 2552t
anatomy of, 131
aorta vs.
in fetal echocardiography, 810
balloon dilation of, 1265
closure of, 285, 1057, 2108-2109
anatomic, 132
coarctation of the aorta and, 1356, *1357,* 1357
mechanism of, 1056
regulation of, 2109-2112
theories relating to, 2112
embryology of, 1055, *1056*
fetal
flow velocity in, 822, *823*
function of, 2108
histology of, 1056
in pulmonary valve atresia with intact ventricular septum, 1108, 1110
intrauterine constriction of
tricuspid regurgitation and, 2011
medical manipulation of, 2108-2125
morphology of, 2109
changes in, after birth, 131-132
persistent patent. *See* Patent ductus arteriosus
prostaglandin production by, 2111
prostaglandins to maintain patency of, 2118-2121
Ductus diverticulum
acute aortic injury vs., 978
Ductus venosus, 99, 283
closure of, 285
morphologic changes in, after birth, 132
Duplication(s)
chromosomal, 177
Duricef (cefadroxil), 2054
Duroziez's sign, 1515
Duty factor (DF), *526,* 526
Dynamic spatial reconstructor, 632-633, 882
Dysautonomia(s)
drug-induced, 340
familial, 339-340
hyperadrenergic, 336-338, 338t
hemodynamic response to Valsalva maneuver in, 333
signs and symptoms of, 330-331, 331t
hypoadrenergic, 338-340, 339t
acute transitory, 340
hemodynamic response to Valsalva maneuver in, 333
signs and symptoms of, 331t
Dyskinesis
defined, 839, 1694
Dysphagia lusoria, 1431
Dyspnea, 673
in pregnancy, 2376
Dysrhythmia(s). *See* Arrhythmia(s)
Dyssynchrony
defined, 1694
Dystrophin, 51-52, *52*
in Becker muscular dystrophy, 52-53

E sign
in coarctation of the aorta, 1360
Early repolarization syndrome, 742, *742*
Eastman-Bixler syndrome, 2429t
Ebstein, Wilhelm, 1134
Ebstein's anomaly, 1134-1144
anatomy of, 1134-1135, *1135*
angiographic views for, 960t
anomalies associated with, 1135
arrhythmogenic right ventricular dysplasia vs., 1637
cardiac catheterization in, 1140-1141, *1141*
clinical features of, 1136t, 1136-1140, *1137-1139*
computed tomography assessment of, *898-900,* 903
defined, 1134
echocardiographic findings in, 1137-1140, *1139*
electrophysiologic evaluation in, 1140-1141
embryology of, *1135,* 1135-1136
epidemiology, etiology and genetics of, 1136
imperforate, 1135
embryology of, 1136
management of, 1142-1144. *See also* Ebstein's anomaly, surgery for
prostaglandin in, 2119
natural history of, 1142
pathophysiology of, 1136
pregnancy with, 2380
pulmonary valve stenosis vs., 1397
radiographic findings in, 703, *706*
surgery for, 1142-1144, *1143*
ventricular arrhythmias after, 1896
with Wolff-Parkinson-White syndrome, 2175
unoperated

ventricular arrhythmias with, 1891-1892
Eccentricity index
for bicuspid aortic valve recognition, 1360-1361
Echo
gradient
defined, 617
in nuclear magnetic resonance
defined, 616
Echo dropout, 531
Echo rephasing
defined, 616
Echo time
defined, 618
Echocardiography
amplitude mode (A-mode), 528, *529*, 768
artifacts in, 530-531, 531t
basic science and technical aspects of, 524-533
brightness mode (B-mode), 528, *529*
computer applications in, *657*, *667*, 667
congenital heart disease diagnosis with, 769-780
contrast, 780, *782*
ventricular septal defect assessment with, 1011
costs and benefits of, 781
coupling material for, 526
display modes for, 528, *529*
Doppler. *See* Doppler echocardiography
during exercise testing, 832
example of clinical examination with, 777-780, *778-780*
fetal, 805-827
cardiac function assessment by, 818-823
heart rate and rhythm evaluation with, 812-818, *814-819*
indications for, 806
instrumentation for, 806
procedure for examination, 807-812
risks and benefits of, 825-826
future directions in, 531-532, 781-782
in planning cardiac catheterization, 948
instrumentation for, 525-526, *526*, 528-531, *529-530*
M-mode, 528, *529*, 768-783
defined, 768
fetal cardiac function assessment with, 818-820, *820*
fetal heart rate and rhythm evaluation with, 812-814, *814*
safety of, 781
ventricular function assessment using, 780
processing of input signals in, 529-530, *530*
segmental approach to cardiovascular assessment with, 769
example of clinical examination, 777-780
three-dimensional, 531-532
two-dimensional, 528, *529*, 768-783
defined, 769
diagnostic accuracy of, 769
Doppler echocardiography with, 538
fetal cardiac function assessment with, 818-820, *820*
safety of, 781
ventricular septal defect assessment with, *1010-1011*, 1010-1011
Ectopia cordis, *1298-1299*, 1298-1299
Eddy current(s), 608, 616
Edecrin. *See* Ethacrynic acid
Edema, 682
cerebral. *See* Cerebral edema
peripheral
in pregnancy, 2377
pulmonary. *See* Pulmonary edema
Edrophonium (Tensilon)
as antiarrhythmic agent, 2134
in supraventricular tachycardia management, 1823
Education
computer programs for, 665-666
congenital heart disease's effect on, 2524-2525
Edwards' syndrome. *See* Trisomy 18
EF-hand conformation
defined, 61
"Egg on a string" appearance
in transposition of the great arteries, *1183*, 1183
Ehlers-Danlos syndrome(s), 2403, 2404t, 2414, *2416*
aortic aneurysm in, 978
cardiac and renal anomalies in, 2430t
hematologic and oncologic problems with, 2329t
molecular basis of, 48-49
orthopedic problems in, 2459
8 sign
in total anomalous pulmonary venous connection, 697, *1159*, 1159
Einthoven, Willem, 510-511, *512*
Einthoven's triangle, 504, *505*
Eisenmenger's complex, 1006
Eisenmenger's syndrome, 1006. *See also* Pulmonary vascular disease
clinical picture and course of, 2000
obstetric anesthesia with, 2390
pregnancy with, 2380
ventricular arrhythmias with, 1892
Ejection click, 687
split first heart sound vs., 1925
Ejection fraction, 227
calculation of
from cine-CT scanning, 883
from digital subtraction angiography, *911*
from equilibrium blood pool imaging, *838-839*, 838-839
from first-pass blood pool imaging, 841, *842*
first-third, 839
normal values for children, 839t
regional, 839
Ejection time(s)
from equilibrium blood pool imaging, 839-840
from first-pass blood pool imaging, 841
in myocardial infarction, 1708
phase analysis of
in equilibrium blood pool imaging, 840
systolic
in aortic valve area calculation, 942t, 943
Elastic recoil
of lungs, 351
Elastic stocking(s)
to prevent pulmonary embolism, 2510
Elastin
lipid deposition in, 482
Electrical alternans
in pericarditis, 1593-1595
Electricity
properties of selected substances, 548t
safety issues, 547-550
Electrocardiograph. *See also* Electrocardiography
artifact due to malfunction of, 758, *759-761*
built-in artifacts in, 758, *759*
cathode-ray, 511-512, *513*
direct-writing, 511, *513*
minimum performance requirements for, 513t, 514-515
main components of, *500*
minimum performance requirements for, 513t, 513-516, *514-515*
optical, 511
safety and electric shock hazards with, 515
transistorized, 512, *513*
Electrocardiography, 713-767
altitude's effects on, 443
ambulatory. *See* Electrocardiography, Holter
artifacts in, 754-765, *755-765*
"built-in," 758, *759*
causes of, 754-758
movement, 503
QRS "seen through", 763, *764*
repetitive, *763*, 763
systematic approach for recognition of, 758-765
atrial epicardial
in arrhythmia diagnosis, *2163*, 2163-2164
basic science aspects of, 500-523
body chemistry changes and, 747-749
body surface mapping, 518-520, *519-520*
central nervous system effects on, 752
computer applications in, *666*, 666-667
computer processing in, 516-518, *517*
definitions of electrical terms in, 502, *503*
drugs' effects on, 749-752
effects of systemic alterations on, 747-754
esophageal
exercise study with, 1737, *1738*
Holter, 1729-1730, *1731-1732*, 2163
in arrhythmia diagnosis, 1727-1728, *1728-1729*, 2162-2163, *2163*
method for, 2166
event recording, 1735-1737
exercise, 830, *833*, 833
after tetralogy of Fallot repair, 1894
esophageal, 1737, *1738*
in arrhythmia diagnosis, 1737-1740, *1738-1741*
in coronary artery disease diagnosis, 2284
in mitral valve prolapse assessment, 1980
in ventricular arrhythmia assessment, 1878-1879
in ventricular extrasystole evaluation, 1957-1958
range of expected heart rate in, 1738t
heart rate on, *715*, 715
hexaxial reference system in, 506, *507*
history of, 510-512, *512-513*
in coronary artery disease diagnosis, 2278-2279
Holter, 1728-1729
esophageal, 1729-1730, *1731-1732*, 2163
findings in asymptomatic children, 1733t
findings in healthy newborns, 1731t
findings in healthy pre-adolescents, 1732t
for selective recording, 1735-1737
in arrhythmia diagnosis, 1730-1735, *1730-1737*
in screening high-risk patients, 1734-1735
in syncope diagnosis, *1943*, 1943
reproducibility of findings, 1734
in chamber enlargement and hypertrophy, 728-733
in connective tissue disease, 754
in interventricular conduction disturbance, 733-740
in ischemia, injury and infarction, 740-747
in malposition of heart, 724-727
in metabolic diseases, 754
in neuromuscular disorders, 752-754

Electrocardiography *(cont.)*
in sinus node function evaluation, 1751-1760, *1752-1763,* 1753t
instrumentation for. *See* Electrocardiograph
leads used for children, 506-508
monitoring of anesthesia with, 2295
normal findings in, 713-724, 714t
age changes in, 713, *714*
nuclear magnetic resonance synchronization with, 871-872
race differences in, 720
sex differences in, 720
signal processing in, 510-516
signal-averaged, 520-521, *521*
in arrhythmia diagnosis, 1740-1741, 2164
skin-electrode interface in, 503-504
standard
in arrhythmia diagnosis, 1727-1728, *1727-1729*
multichannel recording in, *1727,* 1727
surface electrodes in, 502-510
nature and size of, 503
physical principles of, 502-504, *503*
pitfalls in placement of, 509-510, *510-512*
placement of, 504-510, *505-509*
pregel type, *504,* 504
transtelephonic, 1752-1753, *1753*
treadmill. *See* Electrocardiography, exercise
Electrode(s)
defined, 2153
for electrocardiography. *See* Electrocardiography, surface electrodes in
pill
for transesophageal pacing, 2166
ring
defined, 2154
tip
defined, 2154
Electrode jelly(-ies), 503-504
artifacts due to, 509, *510*
Electrode paste(s), 503-504
artifacts due to, 509, *510,* 754, *756*
Electroencephalogram
for monitoring during anesthesia, 2296, 2301-2302
Electrogram(s). *See also* Electrophysiologic testing
in pacing
defined, 2153
Electrolyte(s). *See also* particular electrolytes and disorders
drugs for adjustment of, 2553t
postoperative assessment and management of, 2259
Electromagnetic interference
defined, 2153
Electromagnetic method(s)
blood flow measurement using, 496-497
Electromechanical dissociation
cardiopulmonary resuscitation for
alpha-adrenergic drugs in, 411
calcium in, 411, 418
Electron(s)
interactions of, with matter, *563,* 563
Electron capture, 561
Electron shielding
in nuclear magnetic resonance spectroscopy, *610,* 610-611
Electron transfer flavoprotein deficiency, 1668
Electron transfer flavoprotein dehydrogenase deficiency, 1668
Electron transport chain, *197,* 197
Electron volt(s)
defined, 623-624
Electrophoresis
agarose-gel
in DNA analysis, 21, *23*
pulsed-field gel, 30
Electrophysiologic testing, 1743-1750
equipment for, 1744, *1745*
in bundle branch block evaluation, 1796-1797
in sinus node function assessment, 1763-1772, *1766-1771,* 1772t, 1772-1773
direct recording techniques, 1765, *1766,* 1771-1772
indications for, 1773
indirect techniques, 1765
in supraventricular tachycardia
indications for, 1826
technique of, 1826t, 1826-1832, *1827*
in syncope diagnosis, 1943
in ventricular arrhythmia, 1879-1881, *1882-1883*
indications for, 1743-1744
procedure for, 1744-1749, *1745-1749*
Electrophysiology
cardiac, 294-317
developmental, 308-309
disease's effects on, 310-311
normal, 294-299
Electrostatic theory of contraction, 214-215
Elimination
of drugs, 469t, 469
first-pass, 471
Ellis-van Creveld syndrome, 2404-2405, 2430t
abnormalities of hand in, 678t, 678, 679
orthopedic problems in, 2457
Embolism
after direct-current countershock, 2170
air. *See* Air embolism
cerebral, 2454
during cardiac surgery, 2312
with mitral valve prolapse, 1982, 1983
from cardiac tumors, 1648
in idiopathic dilated cardiomyopathy, 1624
in infective endocarditis, 1563
in rheumatic heart disease
prophylaxis for, 1521
paradoxical
with right-to-left shunt, 1072
peripheral vascular
causes of, 993
pulmonary, 2083, 2509-2510
chest pain due to, 1948
computed tomography assessment of, 897
during pregnancy, 2383
myocardial infarction vs., 1715
with atrial septal defect, 1028
Embolization
therapeutic
agents and devices for, 974, 1479t, 1479, 2202-2208, *2203-2207*
for bone neoplasms, 992
for gastrointestinal hemorrhage, 984
for hemoptysis in cystic fibrosis, 978, *979*
for pelvic and extremity trauma, 992
for renal trauma, 987-988
for vascular malformations, 1479t, 1479
in pulmonary vascular disease management, 2003
partial splenic, 984
Embryo
age estimates for, 71-72, *72,* 72t-73t
chick, 152
folding of, 75-79, *78*
Embryoblast, 72
Embryology, 71-108
experimental, 152-170
techniques used in study of, 71
Emergency(-ies)
"code medication" worksheet, 2555
management of, 2543t-2547t
Emery-Dreifuss muscular dystrophy, 1677, 2319, 2407
molecular basis of, 53
Emetine
cardiotoxicity of, 1673
Employment, 2528-2530. *See also under* particular disorders
counseling on, 2532-2533
discrimination in, 2529
psychological aspects of, 2525
Enalapril (Vasotec), 2090, 2434t, 2549t
dosage adjustment for renal insufficiency, 2440t
effects on pulmonary circulation, 374t, 378
for congestive cardiomyopathy, 2091-2092
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2367
Encainide, 2127t, 2130, 2550t
dosage adjustment for renal insufficiency, 2441t
effects on electrocardiogram, 751
for supraventricular tachycardia, 1825
for ventricular arrhythmias, 1899
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2365-2366
Encephalitis
cerebral abscess vs., 2309
Encephalopathy
AIDS, 1608
Endocardial cell(s)
transformation and migration of, 160, *161-162*
Endocardial cushion(s), 85, *87*
Endocardial cushion defect. *See* Atrioventricular canal defect(s)
Endocardial fibroelastosis, 1624-1626
clinical picture and laboratory findings in, 1625-1626
congestive heart failure due to, 2013
contracted, 1625
diagnosis and differential diagnosis of, 1626
dilated, 1625
gene therapy for, 59
molecular basis of, 54
mumps and, 2472
myocarditis and, 1580-1581
myocarditis vs., 1585
pathology of, *1625,* 1625
prevalence and etiology of, 1625
radiographic findings in, 703, *709*
treatment and prognosis in, 1626
vasodilators for, 2092
Endocardial tube(s), 79
Endocardial-epicardial flow ratio, 261
Endocarditis. *See also* Infective endocarditis
Libman-Sacks
in systemic lupus erythematosus, 1532
Löffler's, 1635
rheumatic, *1491,* 1491
Endocarditis prophylaxis. *See under* Antibiotic prophylaxis
Endocardium
light microscopic features of, 128, *129*
Endocrine disease
cardiac findings and management in, 2491-2496
Endocrinology, 2491-2500
Endocytic cycle theory, 155-156, *156-157*

Endocytosis, 155
End-of-life indicator
  for pacemaker, 2153
Endomyocardial biopsy
  in anthracycline cardiotoxicity diagnosis, 2341
  in myocarditis diagnosis, 1584-1585
  in rejection monitoring, 2236
    staging of findings, 2242
Endomyocardial fibrosis, 1635
Endothelium
  arterial
    denudation of, in atherosclerosis, 485-486
    effects on thrombosis, 486
    functions of, 485-486, 486t
  pulmonary vascular. *See* Pulmonary vascular endothelium
Endothelium-derived relaxing factor, 366
  synthesis of
    shear stress and, 484
Endotoxin(s), 2470
  antisera to
    in septic shock management, 2470-2471
  shock due to
    cardiac manifestations of, 2470-2471
Endotracheal tube(s), 2291
  plugging of
    prevention of, 2254
  position of
    after surgery for congenital heart disease, 711
  removal of. *See* Extubation
  size chart for, 2557
Endralazine, 2090
End-systolic pressure-volume relationship, 238-239, *239*
  contractility and, 227-228, *228-229*
Energy
  defined, 552
  in atom, 559
  sources of
    for exercise, 428-429
Energy metabolism, 191-197
Energy resolution
  in nuclear cardiology, 569
Enflurane
  effects of
    hemodynamic, 2294t
    on electrocardiogram, 751
Engineer(s)
  clinical
    role in medical instrument life cycle strategy, 544-545
Enhancer sequence(s), 16, 18
  defined, 61
Entamoeba histolytica infection
  cardiac manifestations of, 2471
Enterococcus(-i)
  infective endocarditis due to, 1568-1569
    treatment of, 1571-1572
Enterovirus infection(s)
  congenital, 2472
Enthesopathy, 1536
Entrainment, 312-313
Entrance block
  sinus node
    sinoatrial conduction time and, 1769, *1770*
    sinus node recovery time and, 1766-1768, *1768*
Environmental exposure(s)
  hematologic and oncologic problems due to, 2330
Enzyme(s)
  mechanisms of regulation of activity of, 191-192
Eosinophilic leukemia, 1635
Epicardial cell migration, 159
Epicardium
  development of, *103*, 104, 159
Epidemiology, 135-151
  data collection in, 148, 149t
  data management in, 148-149, 149t
  error avoidance in, 149-150
  of congenital heart disease. *See under* Congenital heart disease
  research question formulation in, 141t, 141-142
  study design in, 141-150, 145t
Epilepsy. *See* Seizure(s)
Epimyocardium, 79
Epinephrine, 2069, 2548t
  in cardiopulmonary resuscitation, 411-413
    intratracheal administration, 409
  in myocardial infarction management, 1717
  in neonatal resuscitation, 2478
  in postoperative management, 2257
  in pulmonary disease treatment
    cardiac effects of, 2506
  mechanisms of action of, 2068t
  pharmacology of, 2069
    in hepatic, gastrointestinal or nutritional disorders, 2364
  side effects of, 2069
  use of, in pregnancy, 2385t, 2385
Episilon wave(s)
  in arrhythmogenic right ventricular dysplasia, *1638*, 1638
Epsilon aminocaproic acid
  in cardiopulmonary bypass hemorrhage management, 2344
Epstein-Barr virus
  B lymphocyte proliferations and
    after heart transplantation, 2245, 2247
  infection with
    after heart transplantation, 2245
  Kawasaki disease and, 1552
Erb limb-girdle muscular dystrophy, 1676
Erg
  defined, 565
Error(s)
  in biomedical measurement
    random, 542
    systemic, 542
  in research studies, 149-150
  statistical
    types of, 651
Erythema chronicum migrans
  in Lyme disease, 1537
Erythema marginatum
  in rheumatic fever, 1493, *1494*
Erythrocyte(s). *See* Red blood cell(s)
Erythroderma
  cardiovascular disease with, 2422
Erythrogenic toxin, 1487
Erythromycin, 2059
  anticoagulant interaction with, 2052
  for infective endocarditis prophylaxis
    limits on frequency of use, 1567
  for Lyme disease, 1539
  for rheumatic fever prophylaxis, 1498, 1499
  parenteral dosage for severe infection, 2057t
Erythropoietin
  renal production of, 463
Escape interval
  in pacing
    defined, 2153
Escape rhythm(s), 1952, *1953*
  extrasystole vs., 1955
  in sinus node dysfunction, 1756-1757, *1758-1759*
  normal rates for, 1952t
Esophageal disorder(s), 2357
  chest pain due to, 1948
Esophageal electrocardiography. *See under* Electrocardiography
Esophageal pacing. *See* Pacing, transesophageal
Esophageal spasm, 1948
Esophagitis, 1948, 2357
Esophagography. *See* Barium esophagography
Estriol test, 2390
Estrogen
  fetal
    placental blood flow and, 281-282
Ethacrynic acid (Edecrin), 2102t, 2103, 2548t
  aminoglycoside interaction with, 2052
  dosage adjustment for renal insufficiency, 2441t
  for congestive heart failure, 2016
  pharmacology of
    in hepatic, gastrointestinal or nutritional disorders, 2366
Ethanolaminosis, 1666
Ethmozine, 2550t
  cimetidine interaction with, 2367
  in supraventricular tachycardia management, 1825
Ethyl chloride
  effects on electrocardiogram, 751
Euchromatin, 17
Eukaryote
  defined, 61
Euploidy
  defined, 176
Eustachian valve, 112-113
  formation of, 84
Evan's blue dye, 934
Even-echo rephasing phenomenon, 600, *601*
  defined, 616
Excitability
  of myocardial cell membrane, 297-298, *298*
Excitable gap
  in atrial flutter, 1850
Excitation
  of electrons, *563*, 563
Excitation-contraction coupling, 202-211, *203-204*
  developmental aspects of, 208-210, *209-210*
  in congestive cardiac failure, 247-248, *248*
Exercise, 428-434. *See also* Exercise testing
  cardiovascular responses to, 429-431
    in children, 432t, 432
  coronary artery disease and, 489, 1991, 2281
  heart rate's effect on cardiac output in, 239
  hypertrophy secondary to
    coronary vascular reserve in, 262
  myosin isoforms and, 219
  sources of energy for, 428-429
  tolerance of
    grading of, 674
    in congenital heart disease, 674
  ventilatory responses to
    in adults, 431-432
    in children, 432t, 432
  ventricular tachycardia related to, 1888
Exercise physiologist
  role in cardiac rehabilitation program, 2268
Exercise testing, 828-835
  at start of cardiac rehabilitation program, 2270
  bicycle vs. treadmill for, 829-830
  blood pool imaging with, 841

Exercise testing *(cont.)*
criteria for termination of, 834
electrocardiographic. *See under* Electrocardiography
equipment for, 2269
handgrip dynamometer, 333
in chest pain evaluation, 1950
in sympathetic neuronal function evaluation, 333-334
indications for, 828-829
measurements during, 830-833
methodology for, 829-833
normal values for, 829, 834t
of pulmonary function
in pulmonary vascular disease diagnosis, 2503
procedure for, *833,* 833-835
thallium-201 myocardial imaging with. *See* Myocardial scintigraphy, perfusion
Exit block
in pacing
defined, 2153
sinoatrial, 1757-1759, *1760*
Exocoelomic cavity, 72
Exon(s), 10, *16,* 17
alternative 3′- and 5′-terminal, 20
combinatorial, 19
defined, 61
fusion, 20
mutually exclusive, 19-20
with internal donor and acceptor sites, 20
Expression vector(s), 25
defined, 61
Expressivity
defined, 174
Extracellular fluid
regulation of osmolality of, 459-460
renal regulation of volume of, 456-459
Extraembryonic coelom, 73
Extrasystole(s), 1955-1958. *See also* Premature atrial contraction(s); Premature junctional contraction(s); Premature ventricular contraction(s)
multiform, 1955
Extremity(-ies)
ischemia of, *2453,* 2453
lower
angiography of, 988-993
vascular supply to, 988, *990*
neoplasms of
angiography in management of, 992
trauma to
angiography in assessment of, 990-992, *991*
upper
angiography of, 988-993
vascular supply to, 988, *990*
Extubation
accidental, 2291
postoperative, 2254-2255

Fabry's disease, 1663, 2407, *2418,* 2418
hyperadrenergic dysautonomia due to, 338
molecular basis of, 47
Facial immersion. *See* Diving reflex
Facioauriculovertebral spectrum. *See* Goldenhar's syndrome
Faciocardiorenal syndrome, 2429t
Facioscapulohumeral dystrophy, 1677
Factor VIII. *See* Von Willebrand factor
Factor IX concentrate
hemophilia A treated with
myocardial infarction and, 1713
Failure to thrive, 674. *See also* Growth
Faint. *See also* Syncope
common, 1929-1930, 1931t
Faintness, 1941
Family
adolescent's and young adult's relations with, 2524
in cardiac rehabilitation program, 2269
Family history
in clinical assessment of heart disease, 676-677
in genetic evaluation, 171-172
Family planning. *See* Contraception
Fanconi's syndrome, 678t, 678, 2329t, 2329
Farber disease, 1662
Fascicular block
electrocardiographic findings in, 735-737, *736-737*
Fasting
neonatal
metabolic derangements during, 2481
Fat(s). *See also* Fatty acid(s); Lipid(s)
body
in nutritional assessment, 2356
dietary
absorption of, in heart disease, 2358
cholesterol and, 479
Fatty acid(s), 475, *476*
as energy substrate
during development, 200
essential, 477
esterification of, 475-476
free, in plasma
triglyceride metabolism and, 478
metabolism of, 477-478
cardiac, *194-195,* 194-195, 622-623
positron emission tomography studies of, 622-623
renal, 463
protein synthesis and, 199
Fatty streak, 475, 487t, *487,* 487
Feeding difficulty
in congenital heart disease, 674
Femoral artery
cannulation of, 951
for blood pressure monitoring during anesthesia, 2295
for peripheral vascular angiography, 973, *974*
limb shortening due to arterial trauma from, 988-990, *991*
systolic pressure in, 918
Femoral vein
cannulation of
for monitoring during anesthesia, 2296
in neonate, 1191-1192
technique for, 949
cutdown to, 950
Fentanyl
for induction and intubation, 2297
for obstetric analgesia, 2387t
hemodynamic effects of, 2294t
Ferrimagnetic substance(s), 603-604, *604*
Ferromagnetism, 603, *604*
effects on nuclear magnetic resonance images, 605
Fetal alcohol syndrome, 676t, 676
hematologic and oncologic problems with, 2330
Fetal hydantoin syndrome, 676t, 678t, 2385, 2386t
Fetal rubella syndrome. *See* Rubella, congenital
Fetal trimethadione syndrome, 676t
Fetus
antepartum surveillance of, 2390-2393
indications for, 2390t
circulation of. *See under* Circulation
maintenance of fluid homeostasis in, 282-283
response of, to stress, 2390
with congenital heart disease
parents' reactions to, 2519-2520
Fever, 676
arthritis with
differential diagnosis of, 1497
postoperative, 2261
Fiber
dietary
digoxin interaction with, 2363
Fibrin
in fibrous plaques, 483
Fibrinogen
in fibrous plaques, 483
Fibrinolysin, 1487
Fibroblast growth factor (FGF), 31
Fibroma, 1651-1652
therapy for, 1654
ventricular, *1649,* 1651-1652, *1654*
tachycardia and syncope due to, 1937, *1940*
Fibromuscular dysplasia
renal vascular hypertension due to, 985
Fibronectin(s)
in cell migration, 156, *157,* 163-164
organism adherence to
infective endocarditis and, 1562
Fibrosa
of cardiac valves, 128
Fibrous plaque(s), 475, 487t, *487,* 487
origin of, 487-488
rupture or ulceration of, 488
Fibrous trigone
left, 111
right, 111, *112*
Fick, Adolph, 927
Fick principle
cardiac output calculation from, 495-496, 927
green dye method vs., 937
Fick's law of gas diffusion, 355
Fiedler myocarditis, 1577
Field theory of contraction, 215
Figure-eight sign
in total anomalous pulmonary venous connection, 697, *1159,* 1159
Figure-three sign
in coarctation of the aorta, 703, *1360,* 1360
File manager program(s), 662
Filling time(s)
from equilibrium blood pool imaging, 839-840
from first-pass blood pool imaging, 841
Filtration
x-ray beam
in digital subtraction angiography system, 637-638
Filtration coefficient
increased
pulmonary edema due to, 396-398
pulmonary fluid balance and, 391
Financial problem(s)
in congenital heart disease
adolescents' attitudes toward, 2524
effects on patient's marriage, 2525
siblings' attitudes toward, 2522-2523
Fish oil(s)
atherosclerosis and, 489
Fisher's exact probability test, 653t, 653
FISP (fast imaging with steady precession), 868-869, *870-872*
Fistula(e). *See also* Arteriovenous fistula(e)

arteriopulmonary
patent ductus arteriosus vs., 1065, *1066*
Brescia-Cimino internal
for dialysis access, 992
coronary artery. *See* Coronary artery fistula
Flail mitral valve, 1974
FLASH (fast low-angle shot)
dynamic cardiac imaging with, 869
Flavin adenine dinucleotide
reduced (FADH2)
in citric acid cycle, 196
in lipid metabolism, 195
P:O ratio for, 197
Flecainide, 2127t, 2130-2131, 2551t
cimetidine interaction with, 2367
dosage adjustment for renal insufficiency, 2441t
effects on electrocardiogram, 751
for supraventricular tachycardia, 1825
for ventricular arrhythmias, 1899
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2365-2366
Flint, Austin, 688t
Flip angle
defined, 616-617
Flitter, 1920
Flood field uniformity testing, *569*, 569
Floppy disk(s), 659
Floppy mitral valve, 1974. *See also* Mitral valve prolapse
Flow molding
in cardiac morphogenesis, 166
Flow-related enhancement, *599*, 599-600
Flucytosine, 2061
in posttransplant infection management, 2468
Fluid(s). *See also* Fluid balance
extracellular. *See* Extracellular fluid
in postoperative management, 2259
intravascular
for neonate, 2481-2482, 2482t
system for administering, during anesthesia, 2291-2293
loss of
in neonate, 2482
in weightless environment, 437
retention of
in compensation of congestive cardiac failure, 244-245
Fluid balance
in lung
determinants of, 389-393
placenta in maintenance of, 282-283
pulmonary circulation's role in, 365
renal regulation of, 459-460
Fluoride
in preventive dental program, 2352
requirements for, 2354
Fluorine-18
positron emission tomography using, 620, 622
Fluorocortisone, 2497t
Fluoroquinolone(s), 2060
Fluoroscopy, 551-556
in congenital heart disease diagnosis, 691
instrumentation for, 553-555
safety and protective measures for, 555-556
video signal processing in, 639-640
5-Fluorouracil
cardiotoxicity of, 2341
Flush technique
blood pressure measurement by, 682
Foam cell(s)
in atherosclerosis, 482, 486
Foamy myocardial transformation of infancy. *See* Ventricular tachycardia, incessant, in infants
Fogarty septostomy catheter, *1196*, 1196
Fontan procedure, 2217
altitude and, 447
electrophysiology of arrhythmias after, 2159
for hypoplastic left heart syndrome, 1328-1329
for single ventricle, 1271-1273, *1272-1273*
for tricuspid atresia, 1123-1125, 1124t, *1124*
postoperative complications of, 2262
radionuclide angiographic evaluation of left ventricular function after, 842
Foramen ovale, 85, 283, 1025
closure of
anatomic, 131
functional, 131, 285
patent
right-to-left shunting across, 1026
valve-competent, 1025
valve-incompetent, 1025
Foreign body(-ies)
in heart, 2538
Forssmann, Werner, 946
Fortaz. *See* Ceftazidime
Forward bending test, 2446, *2448*
Forward triangle method
for cardiac output calculation, 936, *937*
Fosfenopril
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2367
Fossa ovalis, *113*, 113
Fourier transformation
defined, 617
Gibb's phenomenon in, 609
in biomedical measurement, 543
in Doppler echocardiography, 539
in nuclear magnetic resonance, 577, *579*
for localization of spectra, 614
for spatial encoding in planar imaging, 590-591, *593*
Fox green dye. *See* Indocyanine green dye
Fractional distribution method
positron emission tomography evaluation of blood flow using, 621
Framingham study, 1989
Frank, Otto, 232
Frank-Starling mechanism, 224, 232-233, *233*
Frank's vectorcardiographic leads, 508-509, *509*
Free erythrocyte protoporphyrin (FEP)
in iron deficiency, 2331
Free induction decay, 576, *579*
defined, 617
Free radical scavenger(s)
effects on postischemic dysfunction, 274-275
for myocardial protection, 271
Free-water clearance, 456
Frequency
angular
defined, 616
resonant
defined, 618
Frequency encoding
defined, 617
Friedman's statistic, 653
Friedreich's ataxia, 1677-1678, 2315-2317, 2407
congestive heart failure due to, 2015
electrocardiographic findings in, 752
hyperadrenergic dysautonomia due to, 338
orthopedic problems in, 2458
Fucosidosis, 1661
Functional residual capacity, 352, 353
Fungus(-i)
infective endocarditis due to, 1570
treatment of, 1572
pericarditis due to, 1592
treatment of, 1597
posttransplant infection due to, 2468
Furosemide (Lasix), 2100-2103, 2102t, 2548t
aminoglycoside interaction with, 2052
complications of, 2102-2103
dosage adjustment for renal insufficiency, 2441t
effects of
hemodynamic, 2100-2101
on serum calcium, 2499
pulmonary, 2101
in congenital heart disease management in neonate, 1961, 1966
in congestive heart failure management, 2016
in persistent pulmonary hypertension management in neonate, 2485
in postbypass management, 2303
in renal failure prevention, 2436
indications for, 2102
metolazone with, 2105
patent ductus arteriosus and, 2101-2102, 2113
pharmacokinetics of, 2102, 2364t
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2366
Fusion complex(es)
in pacing
defined, 2153
multiform premature ventricular contractions vs., 1869
with premature ventricular contractions, 1864-1865, *1867*

Gadolinium
as nuclear magnetic resonance contrast agent, *605*, 873
paramagnetic susceptibility of, 603
Galactosamine-6-sulfate sulfatase deficiency
in Morquio syndrome, 1660
α-Galactosidase A deficiency
in Fabry disease, 1663
β-Galactosidase deficiency
in gangliosidosis, 1663
in Morquio syndrome, 1660
in sialidosis, 1661
Gallamine, 2295t
Gallavardin, L.
on midsystolic clicks, 1973
Gallbladder
hydropic
in Kawasaki disease, 1554-1556
Gallium-67, 564-565
inflammatory disease imaging with, 847-848
Gallium-68
positron emission tomography using, 620
Galvanometer(s)
in electrocardiography, 510-511, *512*
Gamma camera(s), *566*, 566-568
image quality of, *568-569*, 568-569
multiwire proportional, 568, 849
Gamma ray(s), 560
defined, 624
Gamma variate method
for shunt detection, 846
Gammaglobulin
intravenous
in Kawasaki disease management, 1556-1557

Gangliosidosis(-es), 1663
Gangrene
due to postcatheterization arterial thrombosis
management of, 2453
of the newborn, 2453
Gargoylism. *See* Hurler's syndrome
Gas
diffusion of, 355-356
volume of
conversion from ambient temperature and pressure, saturated, to standard temperature and pressure, dry, 929, 930t
Gas exchange. *See* Respiratory gas exchange
Gastric artery embolization
for gastrointestinal hemorrhage, 984
Gastroesophageal reflux, 1948, 2357
Gastrointestinal tract
abnormalities of
with congenital heart disease, 679, 2357-2358
chest pain originating in, 1948-1949
disorders of, 2357-2359
pharmacology of cardiac drugs in, 2363-2368
hemorrhage of
peripheral vascular angiography in management of, 981-984, *985*
ischemia of, 2358-2359
postoperative assessment and management of, 2259-2260
Gastrulation, 152-154, *155*
Gating
in blood pool imaging, 837-838, *838*
in computed tomography, 632
in imaging
defined, 624
Gating mechanism
in distal conduction system, 1787, *1788*
Gaucher's disease, 1662
orthopedic problems in, 2459
Gauss
defined, 617
Gelfoam
embolization using, 974, 1479t
Gene(s), 12-20
alterations in structure of, 16-17
defined, 61
eukaryotic
general features of, *16*
organization of, 15
Gene conversion, 14
Gene library(-ies), 23-25
Gene locus
defined, 61
Gene therapy, 57-59
disorders potentially treatable by, 59, 59t
somatic, 57-58, *58*
technical aspects of, 58-59, *60*
Generator
radionuclide
defined, 624
Genetic code
defined, 61
Genetic counseling, 172-173, 173t. *See also* particular disorders
Genetic evaluation, 171-172
Genetic expression, 14
Genetic linkage
defined, 62
Genetic polymorphism(s)
defined, 62
Genetic syndrome(s). *See also* particular syndromes
with cardiac manifestations, 2397-2413
autosomal-dominant, 2397-2404, 2398t
autosomal-recessive, 2398t, 2404-2407
with cutaneous involvement, 2414-2418
with orthopedic involvement, 2456-2457
X-linked, 2399t, 2407
Genetics
molecular. *See* Molecular genetics
reverse, 27
Genioglossus muscle
in ventilation, 354
Genome
control of, 15-20
posttranscriptional, *18*, 18
transcriptional, 17-18, *18*
translational, 20
defined, 13, 62
repetitive sequences in, 15
Genomic library
defined, 62
Genomic probe(s)
defined, 62
Genotype
defined, 62
Gentamicin, 2056-2057
dosage adjustment for renal insufficiency, 2440t
for infective endocarditis, 1571-1572
parenteral dosage for severe infection, 2057t
vancomycin synergism with, 2058
Gerlach, W., 570
Germ disk, 72
Giant-cell tumor
embolization for, 992
Gibb's phenomenon, 609
Gibson, G. A., 688t
Gibson murmur, 688t
Gigantism, 2495
Glenn anastomosis
for single ventricle, 1271
for tricuspid atresia, 1123
Fontan procedure after, 1125
Glomerular filtration, 451-453
developmental aspects of, 464-465
Glomerular filtration rate
age-related differences in, 464-465, 2099
autoregulation of, 453
determinants of, 452-453
measurement of, 451-452, *452*, 452t
normal range of, 451
Glomerulonephritis
acute poststreptococcal, 2428-2431
cardiac manifestations of, 2428-2431
in infective endocarditis, 2427-2428
systemic hypertension due to, 1993
Glucagon
inotropic effects of, 2068
protein degradation and, 199
Glucocerebrosidase deficiency
in Gaucher's disease, 1662
Glucocorticoid(s). *See* Steroid(s)
Glucose
administration of, during cardiac catheterization, 963
as energy substrate
during development, 199, 200
cardiac uptake of, 192
positron emission tomography studies of, 623
diuretic-induced intolerance of, 2104, 2105
for myocardial protection, 270
in cardiopulmonary resuscitation, 417-418
in intravascular fluid for neonate, 2481
tubular transport of, 454
Glucose-6-phosphate dehydrogenase deficiency
antibiotic-induced hemolysis in, 2049
Glucose-insulin-potassium (GIK)
for myocardial protection, 270
β-Glucuronidase deficiency
in Sly syndrome, 1661
Glutamic-oxaloacetic transaminase (GOT)
in amino acid metabolism, 196
serum (SGOT)
elevation of, in congestive heart failure, 2361
in myocardial infarction diagnosis, 1698, *1698*
Glutamic-pyruvic transaminase (GPT)
in amino acid metabolism, 196
Glutaric acidemia
type II, 1668
Glutathione peroxidase deficiency
selenium deficiency and, 1666
Glycogen
degradation of, 192
synthesis of, 192
Glycogen storage disease
pulmonary stenosis due to, 1397
Type II. *See* Pompe's disease
type III, 1665
type IV, 1665
Glycogèn synthetase, 192
Glycogenolysis, 192
Glycogenosis
generalized. *See* Pompe's disease
Glycolysis, 192-193, *193*
in ischemic myocardium, 1689
Glycoproteinosis(-es), 1661-1662
Glycopyrrolate
premedication with, 2291
Glycosaminoglycan(s)
antiproliferative
smooth muscle cell synthesis of, 484
antithrombotic action of, 486
in atherosclerosis, 482
in neural crest cell migration, 164
Goiter
bruit of
venous hum vs., 1926
intracardiac
right ventricular outflow obstruction due to, 1397
Gold-195m, 564, 849
Goldberger's augmented unipolar limb leads, 506, *507*
Goldenhar's syndrome, 2409-2410, *2410*, 2430t
orthopedic problems in, 2457
Treacher Collins syndrome vs., 2402
Gooseneck deformity
in atrioventricular canal defect, *1047*, 1047
Gore-Tex shunt, *2211*, 2211
for tetralogy of Fallot, 1092
sequelae of corrective surgery after, 2038
nuclear magnetic resonance imaging of, 860
Gorlin correction factor, 943, 944
Gorlin formula, 940-941, 941t, 944
Gosset, Walter Sealy, 650
Gout
pulmonary stenosis due to, 1397
Gower sign, 2317, 2407
Gradient
defined, 617
Gradient coil(s)
defined, 617
Gradient echo
defined, 617
Gradient echo technique(s), 594-595, *596*, 869, *870-872*

Gradient moment nulling, 869
  defined, 617
Gradient refocusing
  in nuclear magnetic resonance angiography, 869-870
Graham Steell's murmur, 688t
  rheumatic aortic insufficiency vs., 1518
Graphics
  computer programs for, 664, *665*
GRASS (gradient recalled acquisition in the steady state)
  dynamic cardiac imaging with, 869
Graves' disease, 2491
  treatment of, 2492
Gray syndrome, 2048, 2058
Great cardiac vein, 126
Great vessel(s). *See also* particular vessels
  computed tomography assessment of, 883-897, *890-896*
  external topography of, 111
Grönblad-Strandburg syndrome, 2417
Ground-Fault Circuit-Interrupter, 550
Growth, 2354-2356
  failure of
    in congenital heart disease, 674, 1966, 2355-2356
  monitoring of, 2354-2355
  of heart, 132
    hormonal effects on, *37*, 37, 39
    in space, 438
    secondary to hemodynamic overload, 36-37, *37*
Growth hormone (somatotropin)
  increased production of
    cardiac effects of, 2495
  myocardial protein synthesis and, 199
Guanabenz
  hypoadrenergic dysautonomia due to, 340
Guanethidine
  effects on pulmonary circulation, 374t, 376
Guanosine monophosphate (GMP), 14
Guanosine triphosphate (GTP)
  in cAMP synthesis, 322
Guide wire(s)
  for peripheral vascular angiography, *974*
  in cardiac catheterization, 950
Guideline
  defined, 546
Guillain-Barré syndrome
  hyperadrenergic dysautonomia due to, 338
G_x
  defined, 617
G_y
  defined, 617
Gyromagnetic ratio
  defined, 617
G_z
  defined, 617

H band, 130, *131*
HACEK coccobacilli
  endocarditis due to, 1570
Haemophilus influenzae
  culture techniques for, 2047
  endocarditis due to, 1570
  pericarditis due to, 1591
    treatment of, 1597
  type b infection
    cardiac manifestations of, 2469
    vaccine for, for asplenic children, 2473
Haemophilus spp. *See also* Haemophilus influenzae
  endocarditis due to, 1570
    treatment of, 1572
Hagen-Poiseuille's equation, 352
Half-life
  biological
    defined, 624
  of drugs, 469t, 469
  physical
    defined, 624
  radioactive, 561-562
Hallucinogen(s)
  syncope due to, 1941
Haloperidol
  in Sydenham's chorea management, 1499
Halothane
  effects of
    hemodynamic, 2294t
    on electrocardiogram, 751
  induction with, 2297
Hamartoma
  Purkinje. *See* Purkinje hamartoma
Hamburger-Hamilton system of classification, 152
Handgrip dynamometer test, 333
Hangout, 686
Haploidy
  defined, 12, 175
Haplotype
  defined, 12, 62
Hardware
  defined, 657
Harrison's groove(s), 683, 1028
Head injury
  hyperadrenergic dysautonomia due to, 338
Headache, 676
Head-up tilt, 335
Health insurance, 2530-2531
Health Maintenance Organization(s) (HMO), 2530
Heart
  anatomy of. *See* Anatomy
  as electric generator, 500-502, *501-502*
  boot-shaped, 703, *1081*, 1081
  clinical examination of, 683-689
  "crisscross", *1240*, 1240
  descent of, into chest, 94-96, *95*
  development of. *See also* Embryology
    in space, 438
    landmarks in, 73t, 74t, *154*
  embryologic lineage of cells of, *153*
  endocrine function of, 2496
  external topography of, *111*, 111
  fetal
    assessment of function of, 818-823
    innervation of, 287
  fibrous skeleton of, 111, *112*
  function of. *See also* Cardiac output
    assessment of, in fetus, 818-823
    diastolic, 248
    myocardial ischemia's effects on, 266-267
    normal renal relationship to, 2425
    nuclear magnetic resonance assessment of, 866, *867*
    regulation of, 231-243
  gross fiber geometry of, 128
  growth of. *See under* Growth
  innervation of, 127
  malposition of. *See* Cardiac malposition; Dextrocardia
  morphologic changes in, after birth, 130-132
  morphologic features of, 127-130
    by electron microscopy, 128-130, *130-131*
    by light microscopy, 128, *129*
  nervous system's interaction with, 325-348
  nonuniformity of, 248
  normal weight of
    age and, 132
  perforation of
    after myocardial infarction, 2283
  rupture of, 2536-2537
  septation of, 82-89, *84*
  transplantation of. *See* Cardiac transplantation
  trauma to. *See under* Trauma
  tumors of. *See under* Tumor(s); particular tumors
  "upstairs-downstairs", *1240*, 1240
Heart beat
  irregular, 1951-1958. *See also* Arrhythmia(s)
Heart disease
  congenital. *See* Congenital heart disease
  diagnosis of
    clinical assessment in, 671-690
  hypertensive, 2433
  ischemic. *See* Coronary artery disease; Myocardial ischemia
  metabolic. *See* Metabolic disease(s)
  psychological aspects of, 2519-2527
  pulmonary. *See* Cor pulmonale
  pulmonary findings with, 2506-2510
  rheumatic. *See* Rheumatic heart disease
  valvular. *See* Valvular heart disease; particular lesions
Heart failure
  compensatory mechanisms in, 2007-2008, 2086-2087
  congestive. *See* Congestive heart failure
  defined, 244, 2007
  diastolic
    mechanisms of, in ischemia, 267
  fetal
    signs of, 806, 820
  high-output, 2007
  isolated right
    in childhood and adolescence, 2014
    in fetus, 2010-2011
    in infant, 2013
    postoperative, 2015
  laboratory test findings in, 2361
  mechanisms of improvement of cardiac performance in, 2087-2088
  molecular basis of, 55-57
  physiology of, 2086-2087
  pressure-overload, 2007
  systolic
    mechanisms of, in ischemia, 267
  volume-overload, 2007
Heart rate. *See also* Arrhythmia(s); particular arrhythmias
  cardiac output and, 239
    in fetus and newborn, 241
    postoperative, 2257-2258
  contractility and, *229*, 230
  control of
    in fetus, 328-329
    in neonate, 329-330
  fetal
    control of, 328-329
    echocardiographic assessment of, 812-818, *814-819*
    monitoring of, 2390-2391
    normal, 1905
  in baroreflex evaluation, 333
  in parasympathetic neuronal function evaluation, 335

Heart rate *(cont.)*
in response to exercise, 430
myocardial oxygen consumption and, 250
normal
age-related changes in, 715
in fetus, 1905
lower limits of, 1755t
on electrocardiogram, *715,* 715
Heart sound(s)
auscultation of, 685t, 685-686
first, 685t, 685, 1920
normal split, 1922t, *1924,* 1924-1925
fourth, 687, 1920
innocent, 1922t, *1924,* 1925
split first heart sound vs., 1925
innocent, 1919-1928, 1922t
defined, 1919
diastolic, 1925
location of, *1924*
production of, 1920
systolic, 1924-1925
tools available for study of, 1920
palpation of, 684
pathologic
location of, *1924*
second, 685t, 685-686, 1920
fixed splitting of, in atrial septal defect, 1029
split, innocent third heart sound vs., 1925
third, 686-687, 1920
innocent, 1922t, *1924,* 1925
Heart transplantation. *See* Cardiac transplantation
Heart tube
asymmetry of
cardiac looping and, 157-158, 158t
looping of, 81-82, *83,* 156-158, 1234-1236, *1235-1236,* 1280
nomenclature of, 80-81, *81-82*
steps leading to formation of, 72-81, *75-82*
Heartburn, 1948
Heat
loss of
mechanisms of, 2480
minimizing, for neonate, 2481
production of
mechanisms of, in neonate, 2480
Heberden, William
on coronary artery disease, 2277
Heerfordt's syndrome, 2421
Height
measurement of
in infant, 2354-2355
nutritional status and, 2355
Hemangiectatic hypertrophy, 1473
Hemangioendothelioma(s)
hepatic, 981
Hemangioma(s)
cardiac, 1652
cardiovascular disease with, 2422, *2423*
defined, 1472
hepatic, 981, *983*
mediastinal
computed tomography assessment of, *884-886*
neoplastic
capillary angioma vs., 1473
Hematocrit
capillary, in neonate
limitations of, 2336
during cardiopulmonary bypass, 2300
Hematology, 2328-2349
Hemiazygous vein, 1468
Hemiblock. *See* Left anterior hemiblock; Left posterior hemiblock
Hemifacial microsomia. *See* Goldenhar's syndrome
Hemiplegia
orthopedic rehabilitation in, 2454-2455
Hemitruncus, 1128
Hemochromatosis, 1673-1674, *1675. See also* Iron, overload of
Hemodialysis, 2437-2438, 2438t. *See also* Dialysis
angiographic evaluation of access for, *992,* 992-993
echocardiographic assessment in, 2432t, 2432
pericarditis and, 2433
Hemofiltration
continuous arteriovenous, 2438t-2439t, 2438-2439
Hemoglobin(s), 290
concentration of
cyanosis and, 672
decline in, in newborn, 291, *292*
normal values for, 2330, *2331*
M, 2335t, 2335
oxygen affinity of, *290,* 290
in fetus, 282
in newborn, 291
Hemoglobin H disease, 2332
Hemoglobin M syndrome(s), 2335t, 2335, 2336
Hemoglobin S/C disease
altitude and, 448
anesthetic complications in, 2335
Hemoglobin S/T
altitude and, 448
Hemoglobinuria
in postoperative renal failure, 2437
Hemolytic anemia
"cardiac", 2342
with prosthetic devices, *2345,* 2345
Hemopericardium
traumatic, 2537
Hemophilia A
treated with Factor IX concentrates
myocardial infarction and, 1713
Hemophilus influenzae. *See* Haemophilus influenzae
Hemorrhage(s)
intracranial. *See* Intracranial hemorrhage
postoperative, 2260
reperfusion-induced, 268
splinter
in infective endocarditis, 2422
subarachnoid
with coarctation of the aorta, 2311
Hemostasis. *See also* Coagulation
alterations of
in cardiac surgery, 2260-2261, 2343-2344
in noncardiac surgery, 2343
Henle's loop(s)
urine concentration in, 454-455, *455*
Heparan sulfate
in endocardial-mesenchymal migration, 160, *162*
Heparin, 2079-2080, 2553t
effects on pulmonary circulation, 379
in cardiopulmonary bypass, 2300
in idiopathic dilated cardiomyopathy
management, 1624
in pulmonary embolism management, 2510
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2367
reversal of, 2300
use of, during pregnancy, 2382
Heparin rebound
cardiopulmonary bypass hemorrhage due to, 2344
Hepatic portoenterostomy
for biliary atresia, 2362
Hepatic vein(s)
anomalous connection of, 1469
nuclear magnetic resonance imaging in, 861
Hepatitis
ischemic, 2360-2361
Hepatoblastoma, 981
Hepatocardiac channel(s), 98-99
Hepatocellular carcinoma, 981
Hepatomegaly, 682-683, 2359
Hering-Breuer reflex, 357
Heritability
defined, 175
Herpes simplex virus
infection with, after heart transplantation, 2245, 2468
myocarditis due to, 1579
Herrick, J. B.
on coronary artery disease, 2278
Hertz
defined, 617
Heterochromatin, 17
Heteroduplex(es)
defined, 62
DNA-RNA, 10, *12*
Heterogeneity
defined, 174
Heterotaxy, 1287-1298. *See also* Asplenia syndrome; Polysplenia syndrome
defined, 1280, 1287-1288
embryology of, 1289
incidence, etiology and genetics of, 1288-1289
Hewett, Sir Prescott
on arteriovenous fistula, 1471
Hexamethonium
effects on pulmonary circulation, 374t, 376
Hexokinase
in cardiac glucose metabolism, 192
Hexosaminidase deficiency
in gangliosidosis, 1663
Hiccough(s)
electrocardiographic artifact due to, 754, *757, 762*
High altitude cerebral edema, 445, 446
High altitude pulmonary edema. *See under* Pulmonary edema
High-density lipoprotein. *See under* Lipoprotein(s)
His bundle
anatomy of, *124,* 124-125, *1786,* 1786-1787
development of, 104
electrophysiologic characteristics of, 1787, *1788*
intraoperative injury to, 2258
Histamine
effects of
inotropic, 2068
on pulmonary circulation, 374t, 376
Histamine receptor(s), 376
Histiocytoid cardimoyopathy. *See* Ventricular tachycardia, incessant, in infants
Histone(s), 15
Histoplasma capsulatum
pericarditis due to, 1592
diagnosis of, 1596
treatment of, 1597
History
in clinical assessment of heart disease, 671-679
birth, 677
family, 676-677

pregnancy, 676
in evaluation of autonomic control of cardiovascular function, 330-331, 331t
in genetic evaluation, 171-172
HIV. *See* Human immunodeficiency virus
HIV-associated embryopathy, 1606-1607
HLA antigen(s)
B-27
in spondyloarthropathies, 1536
defined, 62
in transplantation, 2241
Hodgkin, Thomas, 688t
Hodgkin-Huxley model of sodium channel, 302, *303*
Hodgkin's murmur, 688t
Hogness box. *See* TATA box
Holiday heart syndrome, 1673
Holmes, Andrew F., 1246
Holmes heart, 1250-1251
Holter monitoring. *See under* Electrocardiography
Holt-Oram syndrome, 678t, 678, 1025, 2401
orthopedic problems in, 2456-2457
Homocystinuria, 2406-2407
hand abnormalities in, 678t
hematologic and oncologic problems with, 2329t, 2330
molecular basis of, 47
Homogeneity
defined, 617
Homology
defined, 62
Hope, James
on innocent murmurs, 1919
Horizon(s)
developmental, 71-72, *72*
Hormone(s), 2491. *See also* particular hormones
Hospitalization
adolescent's perceptions of, 2523-2524
child's reactions to, 2521-2522
Hot spot
defined, 62
Hounsfield unit(s), 630
HTLV-III. *See* Human immunodeficiency virus
Human immunodeficiency virus (HIV), 1605-1606, *1606-1607*
infection with. *See also* Acquired immune deficiency syndrome
after heart transplantation, 2245
tests for, 1611
Human leukocyte antigen(s). *See* HLA antigen(s)
Human placental lactogen test, 2390
Human T cell lymphotropic virus type-III. *See* Human immunodeficiency virus
Humeroperoneal muscular dystrophy. *See* Emery-Dreifuss muscular dystrophy
Hunter, John, 2278
Hunter's syndrome, 1659-1660, 2406t, *2417*, 2417
molecular basis of, 47
multiple sulfatase deficiency and, 1663
Huntington's chorea
coronary artery disease in, 2280
Hurler-Scheie syndrome, 1659
Hurler's syndrome, 1656-1659, *1659*, 2406t, 2417-2418
congestive heart failure due to, 2015
molecular basis of, 47
Hutchinson-Gilford syndrome. *See* Progeria
H-V interval, 1796-1797
Hyaline membrane disease
patent ductus arteriosus with, 2487
Hyaluronidase, 1487
for myocardial protection, 270
Hybrid resistance unit(s), 932-933
Hybridization
defined, 62
in DNA analysis, 21
in situ, 29-30
Hydralazine (Apresoline), 2434t, 2549t
dosage adjustment for renal insufficiency, 2440t
effects on pulmonary circulation, 374t, 378
for congestive cardiomyopathy, 2091, *2092*
idiopathic, 1623
for congestive heart failure, 2018-2019, 2020t
with atrioventricular canal, 2094
with ventricular septal defect, *2094*, 2094
for cor pulmonale, 2505
for heart failure after cardiac surgery, 2095
in sinus node dysfunction management, 1779
pharmacology of, 2088t, 2090, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2366-2367
systemic lupus erythematosus and, 1533, 2090
use of, during pregnancy, 2386-2387, 2387t
Hydrochlorothiazide (Hydrodiuril), 2434t, 2548t. *See also* Diuretic(s), thiazide
for congestive heart failure, 2016
pharmacokinetics of, 2102t, 2104
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2366
Hydrocortisone, 2496, 2497t
antenatal
effects on patent ductus arteriosus, 2118
Hydrodiuril. *See* Hydrochlorothiazide
Hydrogen
nuclear magnetic resonance spectroscopy using, 615
Hydrogen bonding
defined, 62
Hydrogen ion(s)
renal tubular secretion of, *460*, 460-461
sources of
from diet and tissue constituents, 460t, 460
Hydrolethalus syndrome, 2405-2406
Hydrops fetalis, 818, 1905-1906, *1907*
heart failure and, 806, 807
in alpha-thalassemias, 2332
intrauterine atrial flutter and, 1851
with atrioventricular block
management of, 815-817
3-Hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase)
in cholesterol synthesis, 479
Hydroxychloroquine
cardiotoxicity from, 1663-1664
5-Hydroxytryptamine. *See* Serotonin
Hydroxyzine (Vistaril), 2553t
for obstetric analgesia, 2387t, 2389
Hyoid artery
formation of, 93
Hyperaldosteronism, 2494-2495
Hyperbetalipoproteinemia
familial. *See* Hypercholesterolemia, familial
Hypercalcemia
electrocardiographic findings in, 747-748
idiopathic. *See* Williams syndrome
syncope in, 1932
with thiazide diuretic therapy, 2016-2017, 2105
Hypercholesterolemia
familial, *44*, 44, 1991
gene therapy for, 59
homozygous, 44, 1991
LDL receptor gene mutations in, 47
monogenic, 480
myocardial infarction in, 1713
Hypercoagulability, 2083-2084
atherosclerosis and, 1991-1992
Hypercyanotic spell(s). *See* Tetralogy spell(s)
Hypereosinophilic syndrome(s), 1635
Hyperfibrinolysis
in cardiopulmonary bypass, 2344
Hyperglycemia
postoperative, 2259
Hyperheparinemia
cardiopulmonary bypass hemorrhage due to, 2344
Hyperkalemia
electrocardiographic findings in, 747, *749*
myocardial infarction vs., 1715
in congestive heart failure, 2016
in renal failure, 2437
emergency therapy of, 2437, 2437t
postoperative, 2259
syncope in, 1932, *1936*
with potassium-sparing diuretics, 2016, 2105-2106
Hyperlipidemia(s). *See* Hyperlipoproteinemia(s)
Hyperlipoproteinemia(s)
classification of, 42-45, 1990-1991
familial
contraceptive choice and, 2372
familial combined, 44, 1991
molecular basis of, 42-47
Type I, 44, 1990-1991
Type IIa. *See* Hypercholesterolemia, familial
Type IIb, 44, 1991
Type III, 44-45, 478, 1991
Type IV, 45, 1991
Type V, 45, 1991
Hypermagnesemia
electrocardiographic findings in, 748
Hypermobility syndrome
benign, 2403, 2404t
Hypernatremia
electrocardiographic findings in, 748-749
Hyperphosphatemia
in renal failure
management of, 2437
Hyperpneic spell(s). *See* Tetralogy spell(s)
Hypersplenism
partial splenic embolization for, 984
Hyperstat. *See* Diazoxide
Hypertension, 1993-1994
acute
emergency treatment of, 2431, 2431t
alpha-adrenergic receptors in, 321
coronary artery disease and, 1990, 2281
heart disease due to, 2433
in coarctation of the aorta, 1358
maintenance therapy for, 2434t
persistent
after coarctation repair, 1373, 2031
portal, 981, *984*
postoperative, 1993-1994
after coarctation repair, 1370, 1993-1994, 2263
pulmonary. *See* Pulmonary hypertension
renal vascular, 985-986, *986*
systolic
with wide pulse pressure, 1993
Hyperthyroidism, 2491-2492
amiodarone-induced, 2493, 2494
atrial fibrillation and, 1860
electrocardiographic findings in, 754
hyperadrenergic dysautonomia due to, 338

Hyperthyroidism *(cont.)*
neonatal
congestive heart failure due to, 2013
treatment of, 2492
Hypertransfusion program
for thalassemia, 2332-2333
Hypertriglyceridemia
familial, 45, 1991
restriction of caloric intake in, 478
Hypertrophic cardiomyopathy, 1626-1634
atrial fibrillation and, 1860
characteristics of, 1617, 1619t
clinical findings in, 1629-1630
coronary artery abnormalities in, 1629
diastolic dysfunction in, 1629
differential diagnosis of, 1633
electrocardiographic findings in, 1630, *1631*
myocardial infarction vs., 1714
etiology of, 1627-1628
fibromuscular subvalvular aortic stenosis vs., 1347
genetic aspects of, 2403-2404
in Friedreich's ataxia, 2316
in pregnancy, 2377, 2378
laboratory findings in, 1630-1633, *1631-1632*
molecular basis of, 54
murmur of, 1630
changes in, in pregnancy, 2377
Still's murmur vs., 1923
myocardial perfusion imaging in, 845
natural history of, 1634
nuclear magnetic resonance imaging in, *862*, 862-863
obstructive, 1628-1629
pathology of, 1626-1627, *1627-1628*
prevalence of, 1627
surgery for, 1633-1634
ventricular arrhythmias after, 1896
syncope in, 1931
systolic dysfunction in, 1628-1629
treatment of, 1633-1634
ventricular arrhythmias with, 1892-1893
Hypertrophy. *See* Cardiac hypertrophy; Ventricular hypertrophy
Hyperuricemia
atherosclerosis and, 1992
with diuretic therapy, 2016, 2105
Hypervagotonia
sinus node dysfunction due to, 1775-1776
management of, 1779
Hyperventilation
in pregnancy, 2376
syncope due to, 1940
T-wave changes in, 741
Hyperviscosity
defined, 2336
Hyperviscosity syndrome(s), 2336-2337
congestive heart failure due to, 2012
diagnosis and management of, 1999
neonatal
clinical manifestations of, 2336
Hypocalcemia, 1668-1669, *1669*
electrocardiographic findings in, 748
hypokalemia vs., 748
in diabetic ketoacidosis, 2495
in DiGeorge syndrome, 2499
patent ductus arteriosus and, 2113
postoperative, 2259
with loop diuretic therapy, 2103
Hypochloremia
with loop diuretic therapy, 2102-2103
Hypoglycemia, 1670
electrocardiographic findings in, 749
postoperative, 2259
syncope due to, 1932, 1939
Hypokalemia
atrial flutter secondary to, 1853
electrocardiographic findings in, 747, *750*
hypocalcemia vs., 748
postoperative, 2259
with loop diuretic therapy, 2102
Hypokinesis
defined, 839, 1694
Hypomagnesemia
after cardiac transplantation, 2314-2315
electrocardiographic findings in, 748
with hypocalcemia, 1669
with loop diuretic therapy, 2103
Hyponatremia
electrocardiographic findings in, 748-749
in congestive heart failure, 2426
postoperative, 2259
with diuretic therapy, 2016, 2102
Hypophosphatemia, 1669
Hypoplastic left heart syndrome, 1316-1333
anatomy of, 1316-1317, *1317-1318*
cardiac catheterization and angiography in, 1322-1324, *1325*
after first stage reconstruction, 1328, *1331*
chromosomal abnormalities with, 1318
clinical features of, 1319-1324, *1320-1325*
congestive heart failure due to, 2012
defined, 1316
echocardiographic findings in, 1319-1322, *1321-1324*
after first stage reconstruction, 1327, *1327-1330*, 1328
electrocardiographic findings in, 1319, *1320*
after first stage reconstruction, 1328, *1330*
embryology of, 1318
epidemiology of, 1318
etiology of, 1318
heart transplantation for, 1329-1331
management of, 1324-1331, 1962
after first stage reconstruction, 1326-1328, *1327-1331*
preoperative care in, 1325-1326
prostaglandin therapy in, 2120
natural history of, 1324
physiology of, 1318-1319
roentgenographic findings in, 695-696, 1319, *1320*
after first stage reconstruction, 1328
surgery for, 1962
clinical caveats for, 2299t
decisions and techniques for, 2220-2222
first stage reconstruction, *1326*, 1326
heart transplantation, 1329-1331, 1962
second stage reconstruction, 1328-1329
Hypotension
intraoperative, 2298
Hypothalamic-pituitary-endocrine axis(-es), 2491, 2492t
Hypothalamus
in cardiovascular regulation, 327
Hypothermia
effects on electrocardiogram, 752, *753*
for cardiac surgery, 273, 2210-2211
circulatory arrest with, 2302
neurologic complications after, 2041
topical, 2302
postbypass, 2303
prevention of
during anesthesia, 2293
during neonatal cardiac catheterization, 1190-1191
during surgery, 2293, 2298
Hypothesis
defined, 644
Hypothyroidism, 2492-2493, 2493t
amiodarone-induced, 2493-2494
congestive heart failure due to, 2013
electrocardiographic findings in, *753*, 754
Hypoventilation
alveolar
cor pulmonale due to, 2504
Hypovolemia
avoidance of
in pulmonary vascular disease patient, 2004
postoperative
management of, 2255-2256
with loop diuretic therapy, 2102
Hypoxemia
chronic, 1996-2006
atherosclerosis and, 1993
consequences of, 1997-1999
defects associated with, 1996-1997
intellectual impairment and, 2310
coronary vascular reserve in, 261-262
effects of hemoglobin concentration in, 1998-1999
persistent neonatal
differential diagnosis of, 2483-2484, 2484t
response to
in neonates, 358
vascular, 1997-1998
Hypoxemic spell(s)
paroxysmal. *See* Tetralogy spell(s)
Hypoxia. *See also* Altitude
alveolar
pulmonary edema due to, 394-395, *395*
chronic
in development of cor pulmonale, 2501-2502
defined, 266, 1686
electrocardiographic findings in, 749
fetal, 2390
bradycardia in response to, 287
pulmonary vasoconstriction due to, 286
nuclear magnetic resonance studies of effects of, 614-615
perinatal
myocardial infarction due to, 1686
response to
age-related differences in, 358
carbohydrate metabolism in, 194
in congenital cyanotic heart disease, 358
lipid metabolism in, 195-196
pulmonary vascular, 369-370
syncope due to, 1939
tissue
prevention of, in neonate, 2482-2483
Hypoxic cardiomyopathy
neonatal, 2479-2480
Hypoxic spell(s). *See* Tetralogy spell(s)
Hypoxic ventilatory response
altitude and, 442
in pregnancy, 446
in cyanotic congenital heart disease, 442
Hysteresis
in pacing
defined, 2153
Hysteria
syncope due to, 1940-1941

I band(s), 130, *131*, 212
Ibuprofen

for myocardial protection, 270
I-cell disease, 1661
ICHD code, 2139, 2153
Idiopathic hypercalcemic syndrome. *See* Williams syndrome
Idiopathic hypertrophic subaortic stenosis. *See* Hypertrophic cardiomyopathy
Iduronate sulfatase deficiency
in mucopolysaccharidosis type II, 1659-1660
Iduronidase deficiency
in mucopolysaccharidosis type I, 1656
IHSS. *See* Hypertrophic cardiomyopathy
Ileus
electrocardiographic findings in, 754
Image intensifier(s)
development of, 635-636
for digital subtraction angiography system, 638
for fluoroscopy, 555
Imaging. *See also* particular modalities
analog vs. digital, 636
cine vs. digital, 640
computer applications in, *657*, *667*, 667
Imipenem (Primaxin), 2056
cilastatin with, 2056
Imipramine (Tofranil)
effects on electrocardiogram, 752
Immotile cilia syndrome, 2511
Immune complex(es)
in infective endocarditis, 1563, 1565
Immune complex disease
rheumatic fever vs., 1497
Immune complex vasculitis
in infective endocarditis, *2422*, 2422
Immune deficiency. *See also* Acquired immune deficiency syndrome
immunization recommendations for, 2472-2473
Immune system, 2239-2241
cellular, 2241
humoral, 2240-2241
Immunization(s)
for heart disease patients, 675, 1966, 2472-2473
immunologic mechanisms in, 2240-2241
Immunoglobulin G
serum levels of, in infants, 2240
Immunosuppression
after heart transplantation, 2235t, 2235, *2243-2244*, 2243-2244
future directions in, 2247-2249, *2248-2249*
neurologic complications of, 2314
Immunosuppressive agent(s). *See also* particular agents
in idiopathic dilated cardiomyopathy management, 1623
in myocarditis management, 1586-1587
Impedance
acoustic, 525
of various media, 525t
electrical
defined, 502, *503*, 2140, 2153
vascular, 224, 235-236
Impedance plethysmography
blood flow measurement using, 497
thoracic
blood flow measurement using, 498
Implant(s). *See also* particular devices
metallic
nuclear magnetic resonance and, 873
Impulse propagation. *See* Conduction
Incubator(s), 2481
Inderal. *See* Propranolol
Indicator dilution method, 933-939
blood flow measurement using, 496
cardiac output calculation from, 496, 934-937, *935-937*, 936t
sources of error in, 936-937
shunt detection with, *937-939*, 937-939
Indium-111
inflammatory disease imaging with, 847-848
myocardial imaging with
in myocardial infarction diagnosis, 1712
Indocin. *See* Indomethacin
Indocyanine green dye, 934
blood flow measurement using, 496
cardiac output determination with, 934-937, *935-937*, 936t
interference from, in spectrophotometric oxygen saturation measurement, 920
shunt detection with, *937-939*, 937-939
Indomethacin (Indocin), 2552t
antiplatelet effects of, 2081
effects on pulmonary circulation, 374t, 377
for patent ductus arteriosus, 1963, 1964-1965, 2114-2118, 2488
animal studies of, 2111
clinical factors affecting initial response to, 2116-2117
clinical trials, 2114-2116
contraindications to, 2118
relation of plasma levels of, to successful treatment, 1964, 2116
pharmacokinetics of, 2116
side effects of, 1964, 2117-2118, 2488
Inductance
defined, 502, 617
Induction
in embryology, 154, 158
Induction/repression method(s)
for detection of foreign DNA in vectors, 25
Infantile cardiomyopathy
idiopathic. *See* Ventricular tachycardia, incessant, in infants
Infantile hypercalcemia. *See* Williams syndrome
Infarct(s)
watershed, of spinal cord
due to cardiac surgery, 2313
Infarction. *See* Myocardial infarction
Infection(s), 2462-2476. *See also* particular disorders
after heart transplantation, 2244-2245, 2246t, 2467-2468, *2468*
bacterial
antimicrobial therapy for, 2047-2051
cardiac manifestations of, 2468-2471
identification of infecting organism in, 2047-2048
susceptibility testing in, 2048
cardiac
in neonates, 2472
complicating cardiac catheterization, 963, 966
dental
prevention of, 2351-2352
hematologic complications of, 2342
involving mediastinum, 2463-2464, *2464*
involving prosthetic devices, 2462-2463
postoperative, 2261
with cardiac manifestations, 2468-2472
cutaneous involvement in, 2421-2422
Infective endocarditis, 1561-1576
arising from dental infection
oral hygiene measures in prevention of, 2351-2352
blood cultures in, 1564-1565, 2047-2048
clinical manifestations of, 1563t, 1563-1564
congestive heart failure due to, 2015
course and prognosis in, 1564
cutaneous manifestations of, 2421-2422, *2422*
dentally-induced bacteremias and, 676, 2351
echocardiographic findings in, 1565-1566
electrocardiographic findings in, 1566
embolism due to, *993*, 993
epidemiology of, 1561-1562
hematologic complications of, 2342
in intravenous drug abusers, 1564, 1569
laboratory investigations in, 1564t, 1564-1565
microbiology of, 1568-1571, 1569t
pathophysiology of, 1562-1563
prophylaxis for. *See under* Antibiotic prophylaxis
prosthetic valve, 1562
organisms causing, 1570
surgery for, 1573
renal complications of, 2427-2428
rheumatic fever vs., 1497
susceptibility to, 1983
after coarctation repair, 2032
after surgery for aortic valve stenosis, 2034
after surgical ligation of patent ductus arteriosus, 2026
after tetralogy of Fallot repair, 1097
after ventricular septal defect repair, 1017, 2030
with atrial septal defect, 1028
with mitral valve prolapse, 1981-1982
with pulmonary valve stenosis, 1398
with tricuspid atresia, 1121
with ventricular septal defect, 1017, 2030
treatment of, 1571-1573, 1572t
with coarctation of the aorta, 1367, 2032
with patent ductus arteriosus, 1062-1063, 2026
Inferior vena cava
anatomy of, 112
anomalies of, 1467-1468, *1468-1469*
blood flow in
Doppler assessment of, 788
development of, 100
echocardiographic assessment of, 774-775
embryology of, 1462-1463, *1465*
interruption of, with azygous continuation, 1468-1469
nuclear magnetic resonance imaging in, 860
surgical significance of, 1469
location of
in echocardiographic diagnosis of atrial situs, 1468, *1468-1469*
obstruction of
after intra-atrial baffle repair of transposition of the great arteries, 2041, 2263
Inflammatory bowel disease
arthritis with, 1536
pharmacokinetics of beta blockers in, 2365
Inflammatory disease, 1483-1613. *See also* particular diseases
imaging of, 847-848
Inflammatory response
atherosclerosis and, 487
Inflammatory syndrome(s)
postoperative. *See* Postperfusion syndrome; Postpericardiotomy syndrome
Influenza
immunization against, 2472-2473
Infundibular septum, 115-116, *116*
Infusion(s)
intraosseous
in cardiopulmonary resuscitation, 410
intravenous, 472
in cardiopulmonary resuscitation, 410

Infusion pump
electrocardiographic artifact due to, 758, *761*, 764
Inheritance
autosomal-dominant, 173
autosomal-recessive, 174
Mendelian, 173-174
defined, 62
multifactorial
basic principles of, 174-175
criteria for, 175
Nora's hypothesis of, 139
rationale for understanding, 171-173
variations in gene expression in, 174
X-linked dominant, 174
X-linked recessive, 174
Injection(s)
intracardiac
in cardiopulmonary resuscitation, 410
Inlet effect, *536*, 536
Inlet segment, 80-81
Inlet septum. *See under* Ventricular septum
Innominate artery
anomalous, 1428
course, treatment and prognosis in, 1444
radiologic examination in, 1433
formation of, 96
normal anatomy of, 1425
Innominate vein(s), 112
Inotropic agent(s), 2065-2078, 2548t. *See also* particular drugs
conditions affecting response to, 2073-2074
in congestive heart failure management, 2017-2018, 2017t-2018t
in hypoplastic left heart syndrome management, 1325
in postoperative management, 2256-2257
mechanisms of action of, 2067-2069
nonglycoside-positive
in idiopathic dilated cardiomyopathy management, 1623
pharmacology and clinical use of, 2069-2073
use of, in pregnancy, 2384-2385, 2385t
Insertion(s)
chromosomal, 177
Instrumentation. *See also under* particular modalities
basic concepts of, 542-543
care, maintenance and quality control programs for, 550-551
codes, standards and regulations for, 545-547
critical care
life cycle of, 543-545
electrical
safety issues, 547-550
parts of system of, 543
Insulin
deficiency of
triglyceride metabolism and, 478
infusion of, for diabetic surgery patient, 2496
protein synthesis and, 199
Insurance. *See also under* particular disorders
counseling on, 2533
disability, 2529-2530
health, 2530t, 2530-2531
life, 2531-2532, 2532t
Intellectual impairment
altitude and, 444
in congenital heart disease, 675, 2310-2311
Intensive care unit
pediatric
design considerations for, 558
Interatrial sulcus, 111
Intercalated valve swelling(s), 89
Intercostal muscle(s)
in ventilation, 354
Interleukin-1 (IL-1), 2240
monocyte adherence to arterial endothelium and, 486
Interleukin-2 (IL-2), 2240
cyclosporine's effects on production of, 2243
in cellular immunity, 2241
Intermediate syndrome, 2282
Intermittent positive-pressure ventilation (IPPV)
for neonate, 2483
Internodal pathway(s), 123
Intersociety Commission on Heart Disease (ICHD) code, 2139, 2153
Intervening sequence(s). *See* Intron(s)
Interventricular conduction delay, 738, *738*, 1796
Interventricular foramen
primary, 81
Interventricular groove, 81
Interventricular septum. *See* Ventricular septum
Interventricular sulcus(-i), 111
Intestine. *See also* Gastrointestinal tract
ischemia of, 2358-2359
thumbprinting of, 2359
Intra-aortic balloon counterpulsation, *2090*, 2090-2091
for failure to wean from cardiopulmonary bypass, 2303
in myocardial infarction management, 1717-1718
Intra-atrial baffle repair. *See* Atrial baffle procedure(s)
Intracellular adhesion molecule (ICAM)
monocyte adherence to arterial endothelium and, 486
Intracranial abscess. *See* Brain abscess
Intracranial aneurysm(s). *See* Aneurysm(s), cerebral
Intracranial hemorrhage
coarctation of the aorta and, 1366-1367
due to cardiac surgery
neurologic complications due to, 2312
symptoms and signs of, 2313
due to ruptured mycotic aneurysm
cerebral abscess vs., 2309
electrocardiographic findings in myocardial infarction vs., 1715
Intracranial pressure
cardiopulmonary resuscitation's effects on, 409
Intrauterine device(s), 2372-2373
Intravascular stent(s). *See* Vascular stent(s)
Intraventricular conduction delay, *738*, 738, 1796
Intron(s), 10, *12*, 17
defined, 62
retained, 20
Intron-exon junction(s)
defined, 62
Inulin
in glomerular filtration rate assessment, 451-452
Inversion (chromosomal), 177
Inversion (nuclear magnetic resonance), 617
Inversion (ventricular). *See* Ventricular inversion
Inversion recovery
defined, 617
Inversion time
defined, 618
Inversion transfer
nuclear magnetic resonance evaluation of reaction kinetics by, 612
Iodoantipyrine
radiolabeled
blood flow measurement using, 495
Ionization, *563*, 563
Ipecac
cardiotoxicity of, 1673
Iridium-191m, 564, 848-849
Iridocyclitis
in juvenile rheumatoid arthritis, 1527
Iron
deficiency of
anemia due to, 2330-2332, *2332*
overload of. *See also* Hemochromatosis
due to chronic transfusion therapy in thalassemia, 2332-2334, 2334t
paramagnetic susceptibility of, 603
effects on nuclear magnetic resonance images, 605
supplemental
for infants, 2354
Iron chelation
in thalassemia management, 2333-2334, 2334t
Irradiation. *See* Radiation
Irritable bowel syndrome, 1948-1949
Ischemia
carbohydrate metabolism in response to, 194
cerebral. *See* Cerebrovascular accident(s); Embolism, cerebral
defined, 266
detection of
by positron emission tomography, 622-623
glycolysis and, 193
intestinal, 2358-2359
limb, 2453, *2453*
myocardial. *See* Myocardial ischemia
nuclear magnetic resonance studies of effects of, *614*, 614-615
Ischemic heart disease. *See* Coronary artery disease; Myocardial ischemia
Ischemic hepatitis, 2360-2361
Ischemic nephropathy
principles of management of, in recovery room, 2436
Ischemic optic neuropathy
cardiac surgery and, 2312-2313
ISIS (image selected in vivo spectroscopy), 614
Isochromosome(s), 177
Isoflurane
hemodynamic effects of, 2294t
Isolated Power System, 550
Isomeric transition, 561
Isomerism
defined, 1281
left. *See* Polysplenia syndrome
right. *See* Asplenia syndrome
Isomyosin(s), *33*, 34, 34t, *35*, 217-218
atrial, 218
changes in
developmental, 218-219, 246, *247*
with cardiac hypertrophy, 36-37, *37*, 246
conduction system, 218
distribution of, 34-35, *35-36*, 218
hormonal effects on, 37, *37-38*
functional regulation of, 219
hormonal control of, 219
regulation of activity of, 220
ventricular, 218
Isoniazid
for tuberculosis, 2060
genetic variation in acetylation of, 2049
systemic lupus erythematosus and, 1533
Isoproterenol, 2070, 2548t

beta-adrenergic receptor responsiveness
evaluation using, 334
effects on pulmonary circulation, 374t, 375
in cardiopulmonary resuscitation, 420
in congestive heart failure management, 2018, 2018t
in postoperative management, 2257
in pulmonary disease treatment
cardiac effects of, 2506
in syncope diagnosis, 1944-1945
in ventricular fibrillation treatment, 1901
mechanisms of action of, 2068t
pharmacology of, 2070
in hepatic, gastrointestinal or nutritional disorders, 2364
side effects of, 2070
use of, in pregnancy, 2385t, 2385
Isosorbide dinitrate
effects on pulmonary circulation, 374t, 377
for congestive cardiomyopathy, 2092
pharmacology of, 2090
Isotope(s)
defined, 559, 624
Isotopic testing. *See* Nuclear cardiology
Isozyme(s)
defined, 62
Ivalon (polyvinyl alcohol foam)
embolization using, 974, 1479t
Ivemark's syndrome, 1288, 2405-2406. *See also* Asplenia syndrome; Polysplenia syndrome
cardiac and renal anomalies in, 2430t

J wave
in hypothermia, 752, *753*
Jaccoud's deformity, 1492
James, T. N.
on Q-T interval, 722
James fiber, 1838. *See also* Lown-Ganong-Levine syndrome
Janeway lesion(s)
in infective endocarditis, 1564, 2422
Jatene operation. *See* Arterial switch procedure
Jaundice
neonatal
diuretic therapy during, 2105
postoperative, 2260
Jenner, Edward, 2278
Jervell-Lange-Nielsen syndrome, 341, 752, 1888-1889. *See also* Long Q-T syndrome(s)
syncope in, 1932
Jugular lymphatic duct, 112
Jugular vein(s)
cannulation of, 950, 2296
origin of, 99
Jugular venous pressure(s), 682
Junctional bigeminy, *1956*
Junctional extrasystole(s). *See* Premature junctional contraction(s)
Junctional rhythm, 1954
Junctional tachycardia. *See* Supraventricular tachycardia

Kallikrein
renal, 458, 464
Kanamycin, 2056
dosage adjustment for renal insufficiency, 2440t
Kaolin-pectin preparation(s)
digoxin interaction with, 2363
Kartagener's syndrome, 1284-1285, 2429t, 2511
Karyotype
defined, 175
normal female, *177*
normal male, *176*
Karyotyping
techniques for, 178
Kasabach-Merritt syndrome, 2343
Kasai procedure
for biliary atresia, 2362
Katz-Wachtel criterion, 731, *732*
in ventricular septal defect, 1009
Kaufman-McKusick syndrome, 2430t
Kawasaki, Tomisaku, 1542
Kawasaki disease, 1542-1560, 2419-2420
arterial thrombosis in, 2084
complications of, 1552-1556, *1553-1556*
cardiovascular, 1552-1554
hepatic and biliary, 1554-1556
congestive heart failure due to, 2013
coronary angiography in, 1554, 1557
coronary artery bypass surgery for, 1558
cutaneous manifestations of, 1543-1545, *1544-1545*, 2420, *2420*
diagnosis of, 1543t, 1546, 2420
differential diagnosis of, 1546-1549
electrocardiographic findings in, 1545, *1546*
epidemiology of, 1542-1543
etiology of, 1549t, 1549-1552
followup in, 1558
history of, 1542
inflammatory disease imaging in, 848
myocardial infarction in, 1554, 1712
electrocardiographic findings in, 746, *749*, *1554-1555*, 1702t-1703t, 1706, 1707t
treatment of, 1557
myocardial perfusion imaging in, 845
pathology of, 1546, *1547-1551*
presentation of, 676, 1543-1546, *1544-1546*
prognosis in, 1558
thrombolytic therapy in, 1718
treatment of, 1556-1558
Kearns-Sayre syndrome, 1668, 2321
Keflex (cephalexin), 2053
Keflin. *See* Cephalothin
Kefzol. *See* Cefazolin
Kelvin's Rule of Measurement, 542
Kent bundle, 738, *739*. *See also* Wolff-Parkinson-White syndrome
concealed, 1838, *1839*
Lown-Ganong-Levine syndrome vs., 1841-1842
surgery for, 2175-2176
tachycardia with, 1834t-1835t, 1841, 1846t, 2174-2175
electrophysiologic evaluation of, 1746, 1840
Kerley B line(s)
in rheumatic mitral stenosis with pulmonary hypertension, 1508
Keshan disease, 1666
Ketamine, 2553t
hemodynamic effects of, 2294t
in cardiac catheterization, 963
for premedication, 948
intramuscular
induction with, 2297
Ketoacidosis
diabetic
management of, 2495
Ketone body(-ies)
metabolism of, 195
3-Ketothiolase deficiency, 1667
Kety-Schmidt method
positron emission tomography evaluation of blood flow using, 622
Keys, Ancel, 1989
Kidney(s), 2425-2444
anomalies of
congenital heart disease with, 679, 2428, 2429t-2430t
calcifications in
with furosemide therapy, 2103
disease of
cardiac manifestations of, 2428-2433
drug excretion by, 470-471
drug interactions involving, 474
drug injury to, 2428
function of. *See* Renal function
in cardiac disease, 2425-2428
in systemic lupus erythematosus, 1530
neoplasms of, 988, *989*
transplantation of
angiography in assessment for, *987*, 987
trauma to
angiography in management of, 987-988
Kienboeck's sign, 2512
Kilobase(s)
defined, 62
Kilobyte
defined, 657
Kinase labeling, 21
Kinin(s). *See also* Bradykinin
renal handling of sodium and, 458
Kirby-Bauer disc sensitivity test, 1571, 2048
Kirchoff's law, 504
Klebsiella spp.
infective endocarditis due to
treatment of, 1572
Klenow fragment
defined, 62
Klinefelter's syndrome, 2328-2329, 2329t
Klippel-Feil syndrome
congenital heart disease in, 678
orthopedic problems in, 2457, *2458*
Kommerell's diverticulum
ductus arteriosus originating from, 1426, 1427
in right aortic arch, 1426, *1427*
right subclavian artery originating from, 1427
Kono procedure, 1523
Korotkoff, Nicolai Sergeevich, 493
Krebs' cycle, *196*, 196
Kreutzer's operation, 1271-1273, 2217
Kruskal-Wallis statistic, 653
Kugel's artery, 1453
Kugelberg-Welander disease
orthopedic problems in, 2459
Kurtosis, 648
Kussmaul's sign, 680-681, 682, 1592
Kwashiorkor, 1669
pharmacology of cardiac drugs in, 2363
Kyphoscoliosis
chest radiographic findings with, 694
electrocardiographic findings in, 727

La antibody
in neonatal lupus erythematosus, 1534
Labetalol
cimetidine interaction with, 2367
use of, in pregnancy, 2386t
Labor and delivery
analgesia for, 2375, 2387t, 2388-2390
fetal surveillance during, 2390-2393
indications for, 2390t
hemodynamics of, 2375t, 2375-2376, 2388
position and, 2388

Labor and delivery *(cont.)*
management of, 2388-2390
Lactate
effects of myocardial accumulation of, 267
fatty acid oxidation and, 196
in pyruvate metabolism, 194
production of
oxygen availability and, 193
Lactic dehydrogenase (LDH)
assay of
in myocardial infarction diagnosis, *1698,* 1698-1699
Lactobacillus spp.
infective endocarditis due to, 1570
Laënnec, René Théophile Hyacinthe
on innocent murmurs, 1919
LAMB syndrome, 2414
Lamor equation, 572, 610
defined, 617
Lamor frequency
defined, 617
Landouzy-Dejerine muscular dystrophy, 1677
Laplace's law, 1513
Largon (propiomazine)
for obstetric analgesia, 2387t, 2389
Laser disk(s)
computer data storage on, 659
Laser Doppler technique(s)
blood flow measurement using, 497
Laser printer(s), 660
Lasix. *See* Furosemide
Lateral plate, 75
Latham, Peter Mere
on innocent murmurs, 1919
Lattice
defined, 617
Laurence-Moon-Biedl syndrome, 678t, 678
LAV. *See* Human immunodeficiency virus
Law
defined, 546
L-CAM (liver-cell adhesion molecule), 156
L-dopa
hypoadrenergic dysautonomia due to, 340
Lead(s) (electrocardiographic)
axis of, 504
bipolar
defined, 504
limb, 504, *505-506*
defined, 504
incorrect positioning of
artifact due to, 509-510, *510-512,* 754, *755-756*
limb
bipolar, 504, *505-506*
hexaxial system representing, 506, *507*
misplacement of, 510, *512*
unipolar, 504-506, *507*
precordial, 506-508, *508*
hexaxial system representing, *508*
misplacement of, 509-510, *511*
standard, 504, *505*
unipolar
defined, 504
limb, 504-506, *507*
vectorcardiographic, *508-509,* 508-509
Lead (metal)
cardiotoxicity of, 1674
Lead(s) (pacing), 2147, *2148,* 2152, 2153
Leading circle model of reentry, 312, 1850
Lecithin-cholesterol acyltransferase (LCAT)
in reverse cholesterol transport, 480
Left anterior hemiblock, 1790-1792, *1793*
causes of, 736-737, 1792
electrocardiographic findings in, 735-737, *736-737*
myocardial infarction vs., 1714-1715
right bundle branch block with, 737, *738*
Left atrial isomerism. *See* Polysplenia syndrome
Left atrial pressure, 918-919
increased
causes of, 393t
pulmonary edema due to, *393,* 393-394
left ventricular pressure and
simultaneous measurement of, 918, *919*
Left atrium
anatomy of, 117, *118*
blood flow in
Doppler assessment of, 791
catheter in, for monitoring during anesthesia
problems with, 2296
enlargement of
electrocardiographic findings in, *732,* 732-733
in fetus
echocardiographic assessment of, 807, *808*
morphologic characteristics of, 1233, 1282
Left bundle branch, *119, 124,* 124-125
anatomy of, *1786,* 1787
electrophysiologic characteristics of, 1787, *1788*
Left bundle branch block, *735,* 735, 1789-1790, *1791-1792*
causes of, 735
incomplete, 1790
electrocardiographic findings in, *735,* 735
myocardial infarction diagnosis in presence of, 1703-1706, 1706t
Left isomerism. *See* Polysplenia syndrome
Left posterior hemiblock, 1792
electrocardiographic findings in, *736-737,* 737
Left subclavian artery
anomalous, 1426, *1427*
course, treatment and prognosis in, 1441-1443, *1443*
echocardiographic identification of, 1434, *1437*
compromise of
after coarctation repair, *2033,* 2033
formation of, 96
isolated, 1426-1427, 1442-1443
Left ventricle
anatomy of, 118-119, *119-120*
double-inlet. *See* Single ventricle
double-outlet, 1213, 1230
dysfunction of, after tetralogy of Fallot repair, 1096
echocardiographic assessment of
in fetus, *808,* 808-810, *810-811*
in Ebstein's anomaly, 1135
morphologic changes in, after birth, 132
morphologic characteristics of, 1233, 1282
on echocardiography, 772, 1242
pathophysiology of failure of
in acute myocardial infarction, 1695
Left ventricular hypertrophy. *See under* Ventricular hypertrophy
Left ventricular inflow
anomalies of
with double-outlet right ventricle, 1223, *1225*
Doppler assessment of, 791, *792*
obstruction of
with atrial septal defect, 1027
with atrioventricular canal defects, 1040
Left ventricular outflow
Doppler assessment of, 791-793, *793*
obstruction of. *See also* Aortic stenosis
after surgery for transposition of the great arteries, 2040
in atrial septal defect, 1027
in hypoplastic left heart syndrome, 1318
in transposition of the great arteries, 1178, 1193, *1194,* 1195
surgical decisions and techniques for, *2219-2221,* 2220-2222
Left ventricular outflow tract
anatomy of, 119
in atrioventricular canal defects, 1037, 1040
echocardiographic examination of, 1044
Left ventricular pressure
diastolic
Doppler estimation of, 798
measurement of, 918
left atrial pressure and
simultaneous measurement of, 918, *919*
systolic
Doppler estimation of, 797, *798*
measurement of, 918
Left ventricular strain pattern, 729, *730,* 730
myocardial ischemia vs., 742
Left ventricular volume
calculation of, from cine angiography, 496
Left-axis deviation, 717-718
left anterior hemiblock vs., 1792
mechanisms of, 736-737
Left-to-right shunt(s)
after Mustard operation for transposition of the great arteries, 2039
age and maturity of patient and, 1000
clinical physiology of, 999-1001
congestive heart failure due to, 2013
defined, 999
detection of
by indicator dilution method, *938,* 938
by oximetry, 919t, 919-920
by radionuclide tracer flow analysis, 846, *846-847*
determinants of magnitude of, 999-1001, 1000t
double
quantitation of, 925-926, *926-927*
inhalation anesthesia with, 2294
intravenous anesthesia with, 2294-2295
obligatory, 1001t, 1001
obstetric anesthesia with, 2390
oximetry in presence of, 920-921
physiological, 925
post-tricuspid, 1000-1001, 1000t-1001t
pretricuspid, 1000, 1000t-1001t
protocol for calculating pulmonary vascular resistance in, 933t
pulmonary edema due to, 394
pulmonary findings with, 2506-2507
quantitation of, 1000t
by Doppler echocardiography, 795-796
by indicator dilution method, 938, *938-939*
by oximetry, 921t, 921-922, *922*
residual
after ventricular septal defect repair, 1016, 2030
thermodilution measurements in presence of, 940
vasodilators for, 2093-2094, *2094*
with atrial septal defect, 1026-1027
with atrioventricular canal defects, 1040-1041
with partial anomalous pulmonary venous connection, 1149-1150
with patent ductus arteriosus, 1058-1060, 1066-1067

with ventricular septal defect, 1005-1007
Lenegre's disease, 1774
Length constant, 301
Length-active tension relationship, 231, *232*
Leopard syndrome, 2400, *2401*, 2414, *2415*, 2430t
pulmonary stenosis in, 1397
renal anomalies in, 2430t
Leptospirosis
cardiac manifestations of, 2469
Leukemia
acute
in Down syndrome, 2328
eosinophilic, 1635
Leukocyte(s)
activated
in reperfusion injury, 269
Leukotriene(s)
in hypoxic pulmonary vasoconstriction, 369-370
in regulation of ductus arteriosus closure, 2112
inactivation of
in lungs, 366
prenatal pulmonary vasoconstriction and, 363-364
Lev, M.
on morphologic designation of cardiac chambers, 1281
Levocardia
defined, 1280
with situs inversus, 1285, 1287, *1287-1288*
Levo-dopa
hypoadrenergic dysautonomia due to, 340
Levo-looping. *See* Cardiac looping
Levothyroxine
for hypothyroidism, 2493
Libman-Sacks endocarditis
in systemic lupus erythematosus, 1532
Lidocaine, 2127t, 2129, 2550t
cimetidine interaction with, 2367
dosage adjustment for renal insufficiency, 2441t
effects on electrocardiogram, 751
in cardiac catheterization, 963
in cardiopulmonary resuscitation, 418-419
in myocardial infarction management, 1718
pharmacokinetics of, 2129, 2364t
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2365
toxic effects of, 2129
use of, during pregnancy, 2385, 2386t
Life insurance, 2531-2532, 2532t. *See also under* particular disorders
Ligament of Marshall, 110
development of, 100
Ligamentum arteriosum, 117
Ligamentum teres, 99
Ligamentum venosum, 99
Light
ductus arteriosus closure and, 2110, 2113
Lightheadedness, 1941
Limb ischemia, 2453, *2453*
Limbus fossa ovalis, *113*, 113
Linea alba
of pulmonary valve, 116
Linkage analysis, *28*, 28
Linoleic acid, 477
Linolenic acid, 477
Lipid(s). *See also* particular lipids
circulatory transport of, 476-477, 477-478, *478*
extracellular accumulation of
in atherosclerosis, 482-483
general properties and physical chemistry of, 475-476, *476*
in arterial wall
physical chemistry of, 483
summary of theories of, *483*, 483
metabolism of, *194-195*, 194-196
atherogenesis and, 475-491
biochemistry of, 42, *42-43*
cellular, in atherogenesis, 481-482
control of, 195-196
diuretics' effects on, 2104, 2105
Lipidemia. *See* Hyperlipoproteinemia(s)
Lipidosis(-es), 1662-1663
isolated cardiac. *See* Ventricular tachycardia, incessant, in infants
Lipodystrophy
generalized, 1678
Lipodystrophy syndrome
Bernardinelli
atherosclerosis in, 1993
Lipogranulomatosis, 1662
Lipoprotein(s), *476*, 476-477, 477t
associations with atherogenesis, 480-481
high-density (HDL)
atherosclerosis and, 481
in reverse cholesterol transport, 480
low-density (LDL)
atherosclerosis and, 480-481
cellular uptake of, 479-480, *480*
hepatic uptake of, 479
in arterial wall, *481*, 481
in cholesterol transport, 479
oxidation of, 482
receptors for, 46-47
structure and metabolism of, 42, *42-43*
transport of
in arterial wall, *481*, 481
triglyceride-rich
atherogenesis and, 481
lipolysis of, *478*, 478
very-low-density (VLDL)
factors increasing secretion of, 478
in lipid transport, 477-478, *478*
Lipoprotein lipase
activity of, in lungs, 366
in lipolysis of triglyceride-rich lipoproteins, 478, *478*
Lipoprotein[a] (Lp[a]), 46, 481
Lipoteichoic acid, 1487
Lisch nodule(s), 2416
Listed
defined, 546
Listeria monocytogenes
infective endocarditis due to, 1570
Literature search
computer-based, 644
Lithium
maternal exposure to
congenital heart disease and, 676t
Liver
acute ischemic disease of, 2360-2361
chronic disease of
causes of, 2361
chronic congestive heart failure vs., 2361-2362
clinical manifestations of, 2361
hypoprothrombinemic, 2344
clinical assessment of, 682-683
congenital anomalies of
with heart anomalies, 2362
disorders of, 2359-2362. *See also* particular disorders
antibiotic dose adjustment in, 2049
pharmacology of cardiac drugs in, 2363-2368
drug metabolism in, 470
drug interactions involving, 474
effects of chronic pressure and volume overload on, 2359-2360
in congestive heart failure, 2009, 2361-2362
in Kawasaki disease, 1554-1556
neoplasms of, 981, *983*
postoperative failure of, 2260
transplantation of
angiography in assessment for, 981
L-looping. *See* Cardiac looping
L_{max}, 231
Load. *See also* Overload
response to, in cardiac morphogenesis, 166-167
Locomotor function
loss of, in weightless environment, 436
Lod score, 28, 62
Löffler's disease, 1635
Long Q-T syndrome(s), 341-342, 1888-1891, 2322-2323
acquired, 1890-1891
body surface map findings in, 519
electrocardiographic findings in, 752, *753*, 1880
molecular basis of, 55
sinus node dysfunction and, 1776
sudden death and, *1913*
syncope in, 1932
Loniten. *See* Minoxidil
Loop-sensor flow meter
intravascular
blood flow measurement using, 497
Lopressor. *See* Metoprolol
Lorazepam
dosage adjustment for renal insufficiency, 2440t
Lorcainide
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2365-2366
Low-density lipoprotein. *See under* Lipoprotein(s)
Lown-Ganong-Levine syndrome, *740*, 740
supraventricular tachycardia in, 1813, 1834t, 1838-1839, *1839*, 1841-1842
electrocardiographic characteristics of, 1835t, 1846t
electrophysiologic criteria for diagnosis of, 1835t
Lp[a] (lipoprotein[a]), 46, 481
Luminal length, 301
Lung(s), 2501-2518
anatomy of, 386-389, *387-388*
chest pain originating in, 1948
compliance of, 351t, *351*, 351-352
frequency dependence of, 353
congestion in
clinical significance of, 683
determinants of fluid balance in, 389-393
development of, 349
elasticity of, 350-351
in congenital heart disease, 350
interstitium of, *388*, 388-389
lymphatics of, 389
in protection against pulmonary edema, 392-393, *393*
morphologic designation of, 1281-1282
nerve supply of, 362
perfusion imaging of, 847
physiology of, 349-359
pump, 2253
zones of, 356-357, *357*
Lung disease. *See* Pulmonary disease

Lung volume(s), *353*, 353-354
Lupus anticoagulant, 1530
Lupus erythematosus
  neonatal, 1533-1536, *2419*, 2419
    clinical presentation of, 1534
    congenital complete atrioventricular block with, 1803, 1804
    etiology of, 1535
    management of mothers and infants with, 1536
    prognosis in, 1535-1536
    risk of development of, in siblings, 1535
    serologic abnormalities in, 1534-1535
  systemic. *See* Systemic lupus erythematosus
Lupus nephritis, 1530
Lupus pernio, 2421
Lutembacher's syndrome, 1026, 1306, 1511, *1512-1514*
  physiology of, 1027
Lyme disease, 1537-1539
  cardiac manifestations of, 1538, 2469
Lymphadenopathy-associated virus. *See* Human immunodeficiency virus
Lymphangiectasis
  pulmonary
    total anomalous pulmonary venous connection vs., 697
Lymphangioma, 1652
Lymphatic(s)
  cardiac
    anatomy of, 126-127
    development of, 103
  development of, *102*, 103
  of lungs, 389
    in protection against pulmonary edema, 392-393, *393*
Lymphatic duct
  right, 112
Lymphoid interstitial pneumonitis
  in acquired immune deficiency syndrome, 1608-1609
Lymphoma(s)
  after heart transplantation, 2245-2247
  cardiac
    myocardial infarction with, 1713
  clonality of
    after heart transplantation, 2247, *2248*
    determination of, 2247
Lyon hypothesis, 485

M. *See* Bulk magnetization vector
M line, 130, *131*
M_0
  defined, 617
MacCallum's patch, 1506
Macintosh operating system, 660-661
Macroaggregated human albumin
  technetium-labeled, 564
    vascular perfusion imaging with, 847
Macrophage(s)
  in atherosclerosis, 482, 486-487
  in humoral immune system, 2240
  origin of, 2239
Macroscopic magnetization vector. *See also* Bulk magnetization vector
  defined, 617
Macroshock, 549
Magnesium. *See also* Hypermagnesemia
  deficiency of. *See also* Hypomagnesemia
    cardiac function and, 2363
  inhibition of calcium release by, 206
  inhibition of mitochondrial calcium uptake by, 207
Magnet(s)
  for nuclear magnetic resonance imaging systems, 605-606, *606*
  permanent, 605
  resistive, 605
  superconducting, 605-606
Magnetic disk(s)
  computer data storage on, 658-659
Magnetic domain(s), 603
Magnetic field(s)
  characteristics of, 586-587, *586-588*
  created by flowing electric current, 586, *587*
  external
    effect of, on nuclear magnetic moment, 571-572, *572*
  inhomogeneities in
    nuclear magnetic resonance artifacts due to, 608
  internal, 602
  strength of
    effect of, on nuclear magnetic moment, 573
Magnetic field gradient(s), 587, *588*
  defined, 617
  in nuclear magnetic resonance imaging systems, 606
  readout, 588
    defined, 618
  spatial localization of nuclear magnetic resonance spectra with, *613*, 613-614
Magnetic resonance imaging. *See under* Nuclear magnetic resonance
Magnetic susceptibility
  defined, 617
Magnetic tape
  computer data storage on, 658
Magnetism, 602-604
  types of, 603-604
Magnetization
  longitudinal
    defined, 617
  transverse
    defined, 619
Magnification Factor, 551
Mahaim fiber(s), 125, 740, *741*
  supraventricular tachycardia with, 1835t, 1842
  ventricular tachycardia vs., 1881
Malabsorption, 2358
  in congenital heart disease, 2355
Maladie de Roger, 1002
Malar flush
  in rheumatic mitral stenosis with pulmonary hypertension, 1507
Malar rash
  in systemic lupus erythematosus, 1529
Malate-aspartate shuttle, 198
Malignancy(-ies). *See also* particular malignancies
  after heart transplantation, 2245-2247, 2246t, *2248*
  cardiac, 1653-1654
  cardiac complications associated with, 2337-2342
Malignant hyperpyrexia, 2303-2304
  management of, 2304t
Malnutrition, 1669-1670
  classification of, 2355t, 2355
  effects of, on cardiac function, 2363
  pharmacology of drugs in, 2363
Malposition. *See* Cardiac malposition; Dextrocardia
Mammary souffle, 1922t, *1926*, 1926
  in pregnancy, 2376
Mandibular artery
  formation of, 93
Mandibulofacial dysostosis, 2401-2402, *2402*
Mangano, D. T.
  on anesthesia for pregnant cardiac patient, 2389
Mannitol, 2106, 2554t
  for myocardial protection, 270
  for renal failure prevention, 2436
Mannosidosis, 1661
Mann-Whitney rank-sum test, 653
Mapleson D system, 2291, *2292*
Mapping
  body surface, 518-520, *519-520*
  electrophysiologic, *1748*, 1748-1749
    catheters for, 1744
    in surgery for accessory pathway tachycardia, *2175-2176*, 2175-2176
    in surgery for atrial ectopic tachycardia, 2178
Marasmus, 1669, 2355
March's factor, 203
Marfan syndrome, 678t, 2397-2399, *2398*, 2399t
  aortic aneurysm in, 978
  cardiac and renal anomalies in, 2430t
  congestive heart failure due to, 2015
  hand abnormalities in, 679
  hematologic and oncologic problems with, 2329t
  mitral valve prolapse in
    ventricular arrhythmias with, 1891
  molecular basis of, 48
  nuclear magnetic resonance imaging in, 856-858, *858*
  orthopedic problems in, 2460
  pregnancy in, 2380-2381
  variation in expressivity in, 174
Maroteaux-Lamy syndrome, 1660-1661, 2406t, 2406
Marriage, 2525
Marrow. *See* Bone marrow
Mask(s)
  for anesthesia, 2291
Mask-and-bag ventilation
  for asphyxiated neonate, 2478
Master's two-step test, 2279
Matter
  defined, 559
  radiation's interaction with, *562-563*, 562-563
Maxam-Gilbert method
  for DNA sequencing, 9, *10*, 23
Mean, 648
Mean corpuscular volume
  normal values for, *2331*
Mean deviation, 649
Measurement
  error in, 542
  requirements for instrumentation for, 542-543
Meckel-Gruber syndrome, 2430t
Median, 648
Median artery
  persistence of, 988
Mediastinitis, 2464
Mediastinum
  infections involving, 2463-2464, *2464*
  lesions of
    computed tomography assessment of, *884-886*, *896*, 897
    nuclear magnetic resonance imaging of, 863
    right ventricular outflow obstruction due to, 1397
Medicaid, 2528, 2531
  Supplemental Security Income and, 2529

Medical history. *See* History
Medical Subject Headings, 644
Medicare
  Social Security Disability Insurance and, 2530
Medulla
  in control of breathing, 357
Mefoxin. *See* Cefoxitin
Megabyte
  defined, 657
Membrane
  cell
    electrical model of, *300,* 300-301
Membrane capacitance
  conduction velocity and, 301
Membrane ionic current(s)
  techniques for studying, 302
Membrane potential
  resting, 294-295, *295*
    of embryonic heart, 308
    of neonatal heart, 309
Membrane responsiveness, 297, *298*
Meningococcal infection
  cardiac manifestations of, 2469
  culture techniques in, 2047
  pericarditis due to, 1591
  vaccine for, for asplenic children, 2473
Mental function. *See* Intellectual impairment
Meperidine (Demerol), 2553t
  dosage adjustment for renal insufficiency, 2440t
  for obstetric analgesia, 2387t, 2388-2389
  premedication with
    for cardiac catheterization, 948
    for surgery, 2291
Mercaptopropionylglycine
  effects on postischemic dysfunction, 274
Mercury
  Kawasaki disease and, 1552
Meromyosin
  heavy, *213,* 213
  light, *213,* 213
Merrill, R. E.
  on statistical significance, 648
Meselson, Matthew, 5
Mesenteric arteritis
  after coarctation repair, 1370
Mesenteric ischemia, 2358-2359
Mesocardia, 1285, *1288*
  defined, 1280
Mesocardium, *80,* 80
  arterial, 110
  venous, 110
Mesoderm, 73, *77*
  differentiation of, 75, *77*
  extraembryonic, 73
  intermediate, 75
  para-axial, 75
Mesothelioma
  of atrioventricular node, 1653
Metabolic acidosis. *See also* Acidosis
  in cardiac arrest
    sodium bicarbonate for, 413-417
    treatment of, 417
  postoperative, 2253, 2261
    management of, 2262
Metabolic disease(s), 1656-1683, 1657t-1658t, 2406-2407. *See also* particular diseases
  cytoplasmic, 1665-1666
  due to cardiotoxins, 1672-1674
  due to substrate and oxygen deficiency, 1669-1671
  electrocardiographic findings in, 754
  electrolyte, 1668-1669
  lysosomal, 1656-1665
  mitochondrial, 1666-1668
  neuromuscular, 1674-1678
  of unknown etiology, 1678
  peroxisomal, 1668
  with extracellular deposition, 1671-1672
Metabolism
  cardiac, 191-201
    cellular compartmentation of, 197-198
    during development, 199-200
    energy substrates for, in developing heart, 247
    final common pathways for, 196-197
    in congestive cardiac failure, 247
    mitochondrial calcium cycle in, 208
    positron emission tomography assessment of, 875
    respiratory control of, 197
  increased, in congenital heart disease
    growth failure and, 2355
Metaraminol
  effects on pulmonary circulation, 373, 374t
Methemoglobinemia, 672, 2335t, 2335-2336
Methicillin, 2052
  dosage adjustment for renal insufficiency, 2440t
  parenteral dosage for severe infection, 2057t
Methimazole
  for hyperthyroidism, 2492
Methoxamine
  effects on pulmonary circulation, 373, 374t
  in cardiopulmonary resuscitation, 411, 412
Methoxyflurane
  effects on electrocardiogram, 751
Methyldopa (Aldomet), 2434t
  dosage adjustment for renal insufficiency, 2440t
  hypoadrenergic dysautonomia due to, 340
  systemic lupus erythematosus and, 1533
  use of, during pregnancy, 2386, 2387t
Methylene blue
  in methemoglobinemia management, 2336
Methylprednisolone, 2497t, 2554t
  for acute rejection, 2498
  for immunosuppression after cardiac transplantation, 2235
Methylxanthine(s)
  mechanisms of action of, 2068
Metoclopramide
  digoxin interaction with, 2363
Metocurine, 2295t
Metolazone (Zaroxolyn), 2100, 2102t, 2105, 2548t
  dosage adjustment for renal insufficiency, 2441t
  pharmacology of
    in hepatic, gastrointestinal or nutritional disorders, 2366
Metoprolol (Lopressor), 2132, 2434t
  hepatitis due to, 2368
  pharmacology of, 2364t
    in hepatic, gastrointestinal or nutritional disorders, 2365
  use of, in pregnancy, 2386t
Metronidazole
  anticoagulant interaction with, 2052
  in brain abscess treatment, 2467
Mexiletine, 2127t, 2129, 2550t
  antacid interaction with, 2367
  dosage adjustment for renal insufficiency, 2441t
  effects on electrocardiogram, 751
  for ventricular arrhythmias, 1898-1899
  gastrointestinal side effects of, 2368
  pharmacology of, 2364t
    in hepatic, gastrointestinal or nutritional disorders, 2365
Mezlocillin, 2053
  parenteral dosage for severe infection, 2057t
Microcomputer(s), 659. *See also* Computer(s)
Microshock, 549
Microsoft Disk Operating System (MS-DOS), 660
Microsoft Windows operating system, 660-661
Microsphere(s)
  radionuclide-labeled
    blood flow measurement using, 256, 494-495, 621
Microvascular hydrostatic pressure
  pulmonary edema due to, 393-396
  pulmonary fluid balance and, 389, *390*
Microvascular oncotic pressure
  decreased
    pulmonary edema due to, 396
  pulmonary fluid balance and, 390
Midazolam
  hemodynamic effects of, 2294t
Middle cardiac vein, 126
Midsystolic click, 687, 1978
  split first heart sound vs., 1925
Migraine
  hyperadrenergic dysautonomia due to, 338
  syncope due to, 1941
Milk spots, 110
Milkmaid's hand
  in Sydenham's chorea, 1493
Miller septostomy catheter, 1196
Miller-Dieker syndrome, 185-186, *186*
Milrinone
  age differences in response to, 2073
  clinical use of, 2072-2073
  in idiopathic dilated cardiomyopathy management, 1623
  pharmacology of, 2072
  side effects of, 2073
Milwaukee brace, *2451,* 2451
Minicomputer(s), 659. *See also* Computer(s)
Minimum alveolar concentration (MAC), 2294
Minimum bactericidal concentration (MBC), 1571, 2048
Minimum inhibitory concentration (MIC), 1571, 2048
Minipress. *See* Prazosin
Minoxidil (Loniten), 2434t
  cutaneous reactions to, 2422
  effects on pulmonary circulation, 374t, 378
  pharmacology of, 2364t
    in hepatic, gastrointestinal or nutritional disorders, 2367
Minute ventilation
  in response to exercise, 431
Mite(s)
  Kawasaki disease and, 1552
Mitochondrial myopathy(-ies), 1667-1668, 2321
Mitochondrion(-a)
  calcium flux by, 207-208
  changes in, during development, 199
  of ventricular myocytes, *130,* 130
Mitomycin C
  cardiotoxicity of, 2341
  doxorubicin cardiotoxicity and, 2339
Mitoxantrone
  cardiotoxicity of, 2341
Mitral atresia
  in hypoplastic left heart syndrome, 1317
  radiographic findings in, 703-707
Mitral commissurotomy
  for mitral stenosis, 1312

Mitral insufficiency, 1313
after myocardial infarction, 1716
after tetralogy of Fallot repair, 1081
Doppler assessment of, 791
in coarctation of the aorta, 2032
in Kawasaki disease, 1554
in systemic lupus erythematosus, 1532
murmur of
changes in, in pregnancy, 2377
Still's murmur vs., 1923
progressive
with mitral valve prolapse, 1982, 1983
radionuclide angiographic evaluation of, 842
rheumatic, 1502-1506
atrial fibrillation and, 1860
cardiac catheterization and angiography in, 1505-1506
clinical manifestations of, 1503-1506
compensation in, *1503,* 1503
echocardiographic findings in, 1504-1505, *1505*
in pregnancy, 2378
pathology of, 1502, *1503*
pathophysiology of, 1502-1503
prognostic indicators in, 1504-1505
radiographic findings in, *1504,* 1504
timing of surgery in, 1522
vasodilators for, *2093,* 2093
Mitral ring
supravalvar. *See* Supravalvar mitral ring
Mitral stenosis
balloon dilation for, 2192-2194, *2195*
cardiac catheterization in, 918, *919*
congenital, 1311-1312
Doppler assessment of, 791
Doppler estimation of valve area in, 799
first heart sound in, 685
in hypoplastic left heart syndrome, 1317
role in etiology, 1318
murmur of
changes in, in pregnancy, 2376
innocent fourth heart sound vs., 1925
obstetric anesthesia with, 2389-2390
opening snap of
innocent third heart sound vs., 1925
pulmonary venous disease secondary to
intrapulmonary veno-occlusive disease vs., 2510
rheumatic, 1506-1511
balloon valvuloplasty for, *1521,* 1521
cardiac catheterization and angiography in, *1510,* 1510-1511
clinical manifestations of, 1507-1509, *1508-1510*
diagnosis of, 1511
differential diagnosis of, 1511
echocardiographic estimation of severity of, 1509
echocardiographic findings in, 1508-1509, *1510*
electrocardiographic findings in, *1508,* 1508
estimation of severity of, 1511
in pregnancy, 2377-2378
pathology of, *1506,* 1506
pathophysiology of, 1506-1507, *1507*
radiographic findings in, 1508, *1509*
surgery for, 1522
syncope due to, 1932
with coarctation of the aorta, 2032
Mitral valve
anatomy of, 117-118, *118-119*
area of. *See* Mitral valve area
balloon dilation of, *1521,* 1521, 2192-2194, *2195*
billowing, 1974
blood flow across
Doppler assessment of, 791, *792*
quantitation of, 795, 943
velocity of, in fetus, 821
cleft
double-orifice mitral valve vs., 1313
congenital abnormalities of, 1311-1313
with coarctation of the aorta, 1356
development of, 89, *93,* 1311
double-orifice, 1312-1313
echocardiographic assessment of, 774
in fetus, 807
flail, 1974
floppy, 1974. *See also* Mitral valve prolapse
identifying features of, 1233
on echocardiography, 1242
in atrioventricular canal defects, 1037, 1038
leaflets of. *See* Mitral valve leaflet(s)
myxomatous degeneration of
in mitral valve prolapse, 336
parachute, 1312
iatrogenic, 1040, 1044
prosthetic, 1313, 1314
replacement of, 1313-1314
rheumatic disease of. *See also under* Mitral insufficiency; Mitral stenosis
arrhythmias in, 1520
mitral valve prolapse vs., 1978
trauma to, 2536
Mitral valve area
Doppler estimation of, 799
echocardiographic measurement of, 1509
Mitral valve leaflet(s)
anterior, 118, *118-119,* 119
systolic anterior motion of, in hypertrophic cardiomyopathy, 1627, 1629, 1630, *1631,* 1632
ballooning of. *See* Mitral valve prolapse
overshooting of. *See* Mitral valve prolapse
Mitral valve prolapse, 336-337, 1973-1986
angiographic findings in, 1981
antibiotic prophylaxis for infective endocarditis in, 336, 1567-1568
arrhythmias with, 336-337, 1982
management of, 1983
chest pain due to, 1949, 1978
clinical course and prognosis in, 1982-1983
clinical features of, 1977-1979
conditions associated with, 1976-1977, 1977t
defined, 1974
diagnostic criteria for, 1974, 1975t
angiographic, 1981
echocardiographic, 1980-1981
discovered after surgical repair of atrial septal defect, 2028
echocardiographic findings in, 1980-1981
electrocardiographic findings in, 742
myocardial infarction vs., 1715
epidemiology and incidence of, 1974-1976
etiology of, 1976-1977
evaluation of, 1983
genetics of, 1976
history of, 1973-1974
hyperadrenergic dysautonomia in, 337
in Von Willebrand's disease, 2343
management of, 1983
midsystolic click with, 687
myocardial infarction and, 1713
pathophysiology of, 1977-1978
pregnancy in, 1983, 2381
primary
defined, 1974
psychoneurotic symptoms in, 1978
pulmonary valve stenosis vs., 1396
rheumatic fever vs., 1498
secondary
defined, 1974
syncope in, 1937, 1978
synonyms for, 1973
unoperated
ventricular arrhythmias with, 1891
Mitral valvotomy
for rheumatic mitral stenosis, 1522
Mitral valvulitis
in rheumatic fever, 1492-1493
Mixed venous blood
defined, 921
in presence of shunt, 921
Mixed venous oxygen tension, 292-293, *293*
M-line protein, 213
Mode, 648
Modem(s), 658, 664
Moderator band, 115-116, *116*
sectioning of
right bundle branch block after, 1788, 1789
Molecular correlation time, 580
Molecular genetics, 3-70
glossary of, 60-63
history and basic concepts of, 3-11
study methods in, 20-30
Momentum
angular
defined, 616
Monge's disease, 446
Monobactam(s), 2055
Monoclonal antibody(-ies)
anti-T cell
in immunosuppression, *2248-2249,* 2248-2249
Monocyte(s)
in atherosclerosis, 486
in humoral immune system, 2240
origin of, 2239
Monosomy, 176
Monosomy 4p, *184,* 184
Monosomy 5p (cri du chat syndrome), 184, 678t, 2429t
Monosomy 9p, 185
Monosomy 13q, 185
Monosomy 17p, 185-186, *186*
Monosomy 18p, 186-187, *187*
Monosomy 18q, *187,* 187
Monosomy 22q11, 187
Monosomy X. *See* Turner's syndrome
Moon facies
pulmonary valve stenosis and, 1387
MOPAC cloning, 26, *27*
Morning after pill, 2373
Morphine, 2553t
dosage adjustment for renal insufficiency, 2440t
for congestive heart failure, 2020
for myocardial infarction, 1717
for paroxysmal hypoxemic spell, 1090
for premedication, 2291
for sedation of infants
dose for, 963
hemodynamic effects of, 2294t
Morphogen(s), 159
Morquio syndrome, 1660, 2406t, 2418
orthopedic problems in, 2459
Morula, 72, *75*

Mosaicism, 176
Mosque sign, *753*, 754
Motion sickness
  in space, 437
Motor development
  in congenital heart disease, 675
Mountain sickness
  acute, 445-446, 446t
  chronic, 446
Moxalactam
  adverse effects of, 2055
M-protein
  of group A streptococci, 1486-1487
MPS. *See* Mucopolysaccharidosis(-es)
MPS cell(s), 1659, *1660*
Mucocutaneous lymph node syndrome. *See* Kawasaki disease
Mucolipidosis(-es), 1661
  type I. *See* Sialidosis
Mucopolysaccharidosis(-es), 1656-1661, 2406t, 2406, *2417*, 2417-2418
  orthopedic problems in, 2459
  type I. *See* Hurler's syndrome
  type II. *See* Hunter's syndrome
Multicore myopathy, 2321
Multiple endocrine neoplasia
  type 2, 2494
Multiple lentigines syndrome. *See* Leopard syndrome
Multiple sulfatase deficiency, 1662-1663
Multislice rotation
  dynamic cardiac nuclear magnetic resonance imaging using, 869
Multivariate analysis
  when to use, 654-655
Mumps
  congenital, 2472
Mural endocardial disease
  idiopathic. *See* Dilated cardiomyopathy, idiopathic
Murmur(s), 687-689, 688t
  age of first appearance of, 687-688
  Austin Flint, 688t, 1515-1516
    rheumatic mitral stenosis vs., 1511
  Carey-Coombs, 688t
    in rheumatic mitral valvulitis, 1493, 1502
  cranial, 689
  description of, 688t, 688
  Gibson, 688t
  Graham Steell's, 688t
    rheumatic aortic insufficiency vs., 1518
  Hodgkin's, 688t
  innocent, 1919-1928, 1922t
    continuous, 1926
    defined, 1919
    diastolic, 1922t, 1925-1926
    history and physical examination in, *1921*, 1921-1922
    in pregnancy, 2376
    prevalence of, 1920-1921
    production of, 1919-1920
    pulmonary artery stenosis vs., 1410
    pulmonary valve stenosis vs., 1396-1397
    rheumatic fever vs., 1498
    systolic, 1922-1924
    tools available for study of, 1920
  "machinery"
  in patent ductus arteriosus, 1060-1061
  of organic heart disease
    changes in, in pregnancy, 2376-2377
  pulmonary
    innocent, *1922*, 1922t, 1923
    pulmonary branch, 1922t, *1923*, 1924
    Still's, 688t, *1922*, 1922t, 1922-1923
Muscle
  cardiac. *See* Cardiac muscle
Muscle fiber(s)
  types of, 429, 430t
Muscle of Lancisi, 114
Muscle of Luschka, 114
Muscle relaxant(s)
  in anesthesia, 2295t, 2295
  reversing effects of, 2295
Muscle strain
  chest pain due to, 1948
Muscular dystrophy(-ies), 1675-1677
  Becker, 1676, 2318-2319, 2407
    molecular basis of, 52-53
  Emery-Dreifuss (humeroperoneal), 1677, 2319, 2407
    molecular basis of, 53
  molecular basis of, 49-53
  myotonic. *See* Myotonic dystrophy
  pseudohypertrophic. *See* Duchenne muscular dystrophy
Mustard operation, 1203, *1204*, 2213. *See also* Atrial baffle procedure(s)
  angiographic views for assessment of, 959t
  arrhythmias after, 1205, 1776, 1852, 2041, 2263
    electrophysiology of, 2159
    sudden death and, 1913
  balloon dilation for venous baffle obstruction after, 2197-2198, *2199*
  complications, residua and sequelae of, 1204-1206, *2039-2040*, 2039-2041, 2263
Mutagen(s)
  defined, 13
Mutation(s), 13-14, *14*
  average rate of, 14
  CpG dinucleotides and, 17
  point, 13-14
Myalgia
  epidemic, 1948
Mycobacterium tuberculosis
  drug therapy for infection with, 2060
  pericarditis due to, 1591-1592
    diagnosis of, 1596
    treatment of, 1597
Mycotic aneurysm
  aortic, 978-980, *980*
  cerebral hemorrhage due to rupture of cerebral abscess vs., 2309
Myectomy. *See also* Ventriculomyotomy
  in hypertrophic cardiomyopathy management, 1633
Myeloproliferative syndrome
  with leukemoid reaction
    with Down syndrome, 2328
    with mosaic trisomy 21, 2328, *2329*
Myoblast fusion, 31
Myocardial abscess
  Staphylococcus aureus, 2469, *2470*
Myocardial blood flow. *See also* Myocardial perfusion
  changes in patterns of, *255*, 255
  determinants of, 254-256
  in cardiopulmonary resuscitation, *408*, 408
  in pulmonary valve atresia with intact ventricular septum, 1110
  left ventricular epicardial
    patterns of, *254*, 254
  left ventricular transmural
    patterns of, *255*, 255
  regional
    measurement of, 256
  regulation of, 256-260
    anatomic factors in, 256-257
    autonomic, 259-260
    hydrostatic forces in, 256
    metabolic factors in, *257*, 257-260
  relative insufficiency of
    myocardial infarction due to, 1686
  reserve, *260-262*, 260-263
  right ventricular
    patterns of, *254*, 254-255
Myocardial cell(s)
  changes in, during development, 199
  cytodifferentiation of
    cardiac looping and, 82
  gene coding potential of, 199
Myocardial contractility. *See* Contractility
Myocardial degeneration
  focal. *See* Ventricular tachycardia, incessant, in infants
Myocardial depressant factor
  in septic shock, 2470
Myocardial function. *See under* Heart
Myocardial hypertrophy. *See* Cardiac hypertrophy; Ventricular hypertrophy
Myocardial infarction, 1684-1722
  acute, 2282-2283
    electrocardiographic findings in, *743*, 744
    endocrine involvement in, 1695-1696
    interventions to minimize infarct size in, 270-271, 1695t
    nuclear magnetic resonance imaging in, 864-866, *866*
    pathophysiology of, 1694-1696
    suggested protocol for, 1719
  after tetralogy of Fallot repair, 2038
  approach to patient in, 1696-1697
  atrial
    electrocardiographic findings in, 1706t, 1706
  cardiac catheterization and angiography in, *1709*, 1709
  causes of, 1685t, 1685-1686, 1712t, 1712-1714
  clinical features of, 1696-1698, 1697t
  complications of, 1715-1716, 2283
  diagnosis of
    suggested protocol for, 1719
  digital subtraction angiography in, 1711-1712
  during pregnancy, 2383
  echocardiographic findings in, 1707-1709
  electrocardiographic findings in, 745-747, *746-749*, 1699t-1700t, 1699-1707, *1701-1702*, 1702t-1703t, *1704-1705*, 1706t-1708t, *1707*
    infarction location and, 1703t, 1703-1706, *1704-1705*
    time course of, 1701-1703
  gross pathology of, 1691-1692, 1692t, *1693*
  hemorrhagic, 268
  histology of, 1692t, 1692-1693, *1693-1694*
  in Kawasaki disease, 1554, 1712
    electrocardiographic findings in, 746, *749*, *1554-1556*, 1702t-1703t, 1706, 1707t
    treatment of, 1557
  in systemic lupus erythematosus, 1531
  indium-111-labeled blood cell imaging in, 1712
  infarct size in, 1695
  laboratory examinations in, 1698t, 1698-1699
  morphologic alterations in, 1691-1694, 1692t, *1693-1694*
  neonatal
    potential factors in, 1707, 1708t

Myocardial infarction *(cont.)*
nuclear magnetic resonance studies in, 1711
pathogenesis of, *1687-1688,* 1687-1690, 1689t, *1690*
pericarditis vs., 745
physical findings in, 1697t, 1697-1698
positron emission tomography in, 1711
presentation of
in adults vs. children, 1684-1685
radionuclide studies in, 1709-1710, *1710,* 1711t
reperfusion injury in, 1691
subendocardial, 1691-1692
syncope due to, 1932
technetium-99m pyrophosphate scanning in, 845, 1709-1710
transmural, 1691
traumatic, *1709,* 1713
treatment of, 1716t, 1716-1719
suggested protocol for, 1719
vasodilators in, 2094-2095
ultrastructural changes in, 1693-1694
with bundle branch block
electrocardiographic findings in, 1703-1706, 1706t, *1707*
with severe pulmonary valve stenosis, 1384-1385
Myocardial injury
electrocardiographic patterns in, 742-745, 1699t, 1700, *1701*
Myocardial ischemia, 266-279
biochemical events in, 1689t, 1689-1690, *1690*
effects of
in immature hearts, 275
on myocardial function, 266-267
electrocardiographic patterns in, 742, 1699t, 1700, *1701*
exercise stress testing in, 1709
global, 1684
irreversible
mechanisms of, 1690t, 1690-1691
nuclear magnetic resonance imaging in, 864
positron emission tomography in, 874-875
regional, 1684
reversibility of, 1687
spectrum of, 1684
stress-induced
myocardial perfusion scanning for detection of, 843-844, 1710
subendocardial. *See* Subendocardial ischemia
subepicardial
electrocardiographic findings in, 742
syncope due to, 1932
transmural
electrocardiographic findings in, 742
Myocardial necrosis
electrocardiographic patterns in, 1699t, 1700
patterns of, 1693
Myocardial oxygen consumption
at rest, 251t
basal, 250
clinically useful indices of, 253t, 253
determinants of, 250-253
for external work, 251, *251-252*
for internal work, 251-253
heart rate and, 250-251
in fetus, 199-200
of electrical activation, 250
Myocardial perfusion. *See also* Myocardial blood flow
assessment of. *See also under* Myocardial scintigraphy
by digital subtraction angiography, 907-908
with positron emission tomography, 875
Myocardial scintigraphy
infarct-avid, 845
in myocardial infarction diagnosis, 1709-1710, 1711t
perfusion, *843-844,* 843-845
in coronary artery disease diagnosis, 2284
in myocardial infarction diagnosis, *1710,* 1710, 1711t
Myocardial sinusoid(s)
in pulmonary atresia with intact ventricular septum, 1109
myocardial infarction due to blood flow into, 1686
Myocarditis, 1577-1589
arrhythmias in, 1583, 1883
management of, 1586-1587, 1888
causes of, 1577, 1578t
clinical presentation of, 1582-1583
defined, 1577
diagnosis of, 1583-1585
differential diagnosis of, 1585
echocardiographic findings in, 1582, 1583-1584
electrocardiographic findings in, *744,* 744, 1583
endocardial fibroelastosis and, 1580-1581
endocardial fibroelastosis vs., 1626
epidemiology of, 1578-1579
Fiedler, 1577
giant cell, 1582
gross and microscopic findings in, 1580-1582
immunopathogenesis of, 1579-1580, *1581*
in juvenile rheumatoid arthritis, 1529
in systemic lupus erythematosus, 1531
incidence of, 1577-1578
molecular basis of, 57
neonatal
congestive heart failure due to, 2012
nuclear magnetic resonance imaging in, 1584
pathology of, 1579-1582, *1581*
pathophysiology of, 1582
prognosis in, 1587
pulmonary stenosis due to, 1397
radionuclide imaging in, 847-848
rheumatic, 1490-1491, 1493
rheumatic fever vs., 1498
screening for, 1584
treatment of, 1585-1587
with steroids, 2497
ventricular extrasystole and, 1957
Myocardium
autonomic innervation of, 318
cellular disarray in
in hypertrophic cardiomyopathy, 1627, 1628
disease of, 1615-1722. *See also* particular diseases
chest pain due to, 1949
protection of, 270-276
current problems and future directions in, 275-276
during cardiopulmonary bypass, 2302
in immature hearts, 275
intraoperative, 272-273
stunned, 266, 273-275, *275*
Myoclonus-cherry red spot syndrome, 1661
Myocyte(s)
atrial, 130
cardiac
cell division by, 30, 165
irreversibly injured
explosive swelling of, 267, 268
reperfusion's effects on, 267-268
ischemic swelling of, 268
ventricular
electron microscopic features of, 128-130, *130-131*
Myocytolysis, 1693
Myofibril(s)
electron microscopic features of, 130
Myogenesis
molecular regulation of, 31-32, *32-33*
Myopathy(-ies). *See also* particular disorders
congenital, 2320-2321
mitochondrial, 1667-1668, 2321
Myopotential(s)
defined, 2153
Myosin, 32-37. *See also* Actomyosin complex
composition of, 32-34, *33*
developmental regulation of, 35-36
in thick filaments, 130, *131,* 1065, *2066*
isozymes of. *See* Isomyosin(s)
phosphorylation of
in actomyosin complex regulation, 216
structure of, *213,* 213
Myosin antibody
in myocardial infarction diagnosis, 1710
Myosin heavy chain(s) (MHC)
cardiac
distribution of, 34, *35-36*
developmental changes in, 218-219
developmental regulation of, 35-36
isoforms of, *33,* 34, 34t, *35*
Myosin light chain(s) (MLC)
cardiac
distribution of, 34-35
developmental changes in, 219
isoforms of, *33,* 34
Myotonia, 2319
defined, 2403
Myotonic dystrophy, 1677, 2319-2320, 2403
congenital, 2320
electrocardiographic findings in, 754
molecular basis of, 53
neonatal, 2403
Myotubular myopathy. *See* Centronuclear myopathy
Myxoid dysplasia
aortic valve stenosis due to, 1335
Myxoma, 1652-1653
left atrial
nuclear magnetic resonance imaging of, *863*
rheumatic mitral stenosis vs., 1511
syncope due to, 1932
right ventricular
pulmonary stenosis due to, 1397

NADH. *See* Nicotinamide-adenine dinucleotide, reduced
NADH-CoQ reductase deficiency, 2321
Nadolol (Corgard), 2132, 2434t
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2365
Nafcillin, 2052
dosage adjustment for renal insufficiency, 2440t
parenteral dosage for severe infection, 2057t
Nalidixic acid, 2060
Naloxone (Narcan)
in obstetric management, 2389
NAME syndrome, 2414
Narcan (naloxone)
in obstetric management, 2389
Narcotic(s). *See also* particular drugs
dosage adjustment for renal insufficiency, 2440t
for obstetric analgesia, 2388-2389

for premedication, 2291
syncope due to, 1941
Narula method
for sinoatrial conduction time assessment, 1770-1771, *1771*
Nasogastric tube feeding, 2356
National Rehabilitation Act of 1973, 2528-2529
Natural killer (NK) cell(s), 2242
in myocarditis pathogenesis, 1579
N-CAM (neural-cell adhesion molecule), 156
in neural crest cell migration, 163
Near-syncope, 1941
Nebulin, 51
Necrotizing enterocolitis
postoperative, 2259-2260
Neisseria gonorrhea
infective endocarditis due to, 1570
Neisseria meningitidis. *See* Meningococcal infection
Nemaline myopathy, 1677, 2321
Neomercazole
myocarditis and, 1582
Neomycin, 2056
digoxin interaction with, 2363
Neonate(s), 2477-2490
arterial thrombosis in, 2488-2489
asphyxiated
resuscitation and stabilization of, 2478-2480
basic respiratory care for, 2482-2483
control of thermal environment of, 2480-2481
critically ill
vasodilators in management of, 2095-2096
metabolic management of, 2481-2482
transport of
to cardiac catheterization laboratory, 948-949
with congenital heart disease, 2483-2486
parental reactions to, 2520-2521
Neostigmine, 2554t
Neosynephrine. *See* Phenylephrine
Nephroblastoma. *See* Wilms' tumor
Nephrology, 2425-2444. *See also* Kidney(s); Renal function
Nervous system. *See also* Autonomic nervous system; Central nervous system
heart's interaction with, 325-348
Netilmicin, 2056
Neural crest, 160-161, *162*
ablation of
heart defects and, 162-163, *164*
cardiac, 161
cell migration from, 161, 163t, *164*
in cardiac development, 160-164
Neural fold(s), 73
Neural groove, 75
Neural plate, 73
Neural tube, 75
α-Neuraminidase deficiency
in sialidosis, 1661
Neuroblastoma
cutaneous manifestations of, 2421
Neurofibromatosis, 2414-2416, *2416*, 2430t
hematologic and oncologic problems with, 2329t, 2330
pulmonary stenosis due to, 1397
renal anomalies in, 2430t
renal vascular hypertension due to, 985, *986*
Neurologic disorder(s)
after hypothermia, 2041
in congenital heart disease, 2305-2315
with cardiac involvement, 2315-2321
Neuromuscular disorder(s), 1674-1678. *See also* particular disorders
cor pulmonale due to, 2504
electrocardiographic findings in, 752-754
Neutrophil(s)
in acute lung injury, 367-368, 368t
Newman, T. B.
on causation of congenital heart disease, 139
Nick translation
defined, 62
DNA labeling using, 21
Nicotinamide-adenine dinucleotide
reduced (NADH)
in carbohydrate metabolism, 193, 194
in citric acid cycle, 196
in lipid metabolism, 195
intracellular transfer of, 198
P:O ratio for, 197
Nidsoldipine
mechanism of action of, 305
Niemann-Pick disease, 1662
Nifedipine (Procardia), 2434t, 2552t
cimetidine interaction with, 2367
dosage adjustment for renal insufficiency, 2440t
effects of
on abnormal automatic rhythms, 314
on pulmonary circulation, 374t, 378-379
for congestive heart failure, 2019, 2020t
for cor pulmonale, 2505
for hypertrophic cardiomyopathy, 1633
for myocardial protection, 271
for pulmonary hypertension, 2002
mechanism of action of, 305
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2366
sublingual
in coronary artery disease management, 2285
Nipride. *See* Nitroprusside
Nisentil (alphaprodine)
for obstetric analgesia, 2387t
Nitrate(s)
effects on pulmonary circulation, 374t, 377
Nitrendipine
effects on pulmonary circulation, 374t, 378-379
mechanism of action of, 305
Nitrite(s)
effects on pulmonary circulation, 374t, 377
Nitrogen-13
positron emission tomography using, 620, 874-875
Nitroglycerin, 2549t
effects on pulmonary circulation, 374t, 377
for myocardial protection, 270-271
in congestive heart failure management, 2019, 2020t
in coronary artery disease management, 2285
in heart failure management after cardiac surgery, 2095
in management of critically ill neonates, 2096
in myocardial infarction management, 2095
in pulmonary vascular disease management, 2003
pharmacology of, 2088t, 2090
sublingual
in coronary artery disease management, 2285
transdermal, 2285
Nitroprusside (Nipride), 2549t
dosage adjustment for renal insufficiency, 2440t
effects on pulmonary circulation, 374t, 377
for congestive cardiomyopathy, 2092
for congestive heart failure, 2019, 2020t
for heart failure after cardiac surgery, *2095*, 2095
for hypoxic cardiomyopathy, 2479
for mitral regurgitation, *2093*, 2093
for myocardial infarction, 1717, 2094, 2095
for myocarditis, 1586
for persistent pulmonary hypertension in neonate, 2486
for postoperative afterload reduction, 2256
for shock in critically ill neonates, 2096
pharmacology of, 2088t, 2088-2089
in hepatic, gastrointestinal or nutritional disorders, 2367
toxicity of, 2088-2089
use of, during pregnancy, 2387t, 2387
Nitrous oxide
halothane with
for induction, 2297
hemodynamic effects of, 2294t
interaction of, with volatile anesthetics, 2294
Nodal rhythm, 1954
Nodulus(-i) Albinii, 114
of mitral valve, 118
Nodulus Arantii, 116, 1335
Nodulus Morgagni, 116
Nonbacterial thrombotic vegetation
in infective endocarditis pathogenesis, 1562-1563
Non-stress test, 2391
Nonuniformity
in congestive cardiac failure, 248
Noonan's syndrome, 2399-2400, *2400*
angiocardiographic appearance of, 1395
congenital heart disease in, 677t, 1397
congestive heart failure due to, 2015
endocrine abnormalities in, 2498t
molecular basis of, 54
orthopedic problems in, 2457
pulmonary artery stenosis in, 1410
Nora, J. J.
on causation of congenital heart disease, 139
No-reflow phenomenon, 268
Norepinephrine, 2069, 2548t
effects on pulmonary circulation, 373, 374t
in myocardial infarction management, 1717
mechanisms of action of, 2068t
metabolism of
in lungs, 366
pharmacology of, 2069
in hepatic, gastrointestinal or nutritional disorders, 2364
plasma levels of
in response to standing and exercise, 333-334
release of
alpha-adrenergic receptors in regulation of, 321
side effects of, 2069
Northern blotting, *9*, 9, 25
defined, 62
Northwest axis, 718
Norwood procedure, 2222
for hypoplastic left heart syndrome, 1962
for subaortic stenosis in single ventricle, 1271
Notochord
definitive, 73
Notochordal process, 73, *77*
Nubain
for obstetric analgesia, 2387t
Nuclear cardiology, 836-851. *See also* Blood pool imaging; Myocardial scintigraphy
basic science aspects of, 559-569
computer applications in, 667
future directions in, 848-849
risks and benefits of, 848

Nuclear cardiology *(cont.)*
techniques for, 836-848
types of studies, 836
Nuclear fission, 561
Nuclear magnetic moment, *571,* 571
bulk magnetization vector of, *573,* 573-574
effect of external magnetic field on, 571-572, *572*
effect of radiofrequency electromagnetic radiation on, 575, *576*
Nuclear magnetic resonance (NMR), 570-619
anatomical evaluation with, 853-855, *855*
angiography using, 869-871, 994
application in particular disorders, 855-866
basic physical principles of, 571-576, *571-578*
blood flow measurement using, 498, 602
cardiac functional assessment by, 866, *867*
characteristics of spectra in, 612
chemical shift in, 581
imaging using, 871
clinical
techniques of, 866-873
clinical aspects of, 852-874
continuous wave, 581-582
diamagnetic substances' effects on, 604
energy levels of, *573,* 573
enhancement of contrast on
with paramagnetic agents, 872-873
ferromagnetic substances' effects on, 605
glossary of terms, 616-619
hazards of and contraindications to, 873-874
history of, 570-571
imaging with, 586-595, 852-853
artifacts in, 604-605, 608-610
blood flow artifact in, 601-602, 609-610
blood flow effects in, 598-600, *599-601*
cardiac synchronization in, 600-601, *601,* 871-872
drawbacks of spin echo method, 594-595
dynamic cardiac, 869, *870-872*
echo-planar method, 595, *597*
effects of sample magnetic properties on, 604-605
gradient echo methods, 594-595, *596-597,* 869, *870-872*
half-Fourier, 594
line methods, 588-589, *590*
magnetic field and radiofrequency pulse characteristics important to, 586-587
methods of, 588-592, *590*
motion artifact in, 600-602, *601,* 610
motion effects in, 595-598, *598*
multiple line acquisition methods, 595, *597*
multislice, *590,* 591, *594*
planar methods, 589-591, *590-594,* 592, *596*
planes used in, *853-854*
point methods, 588, *590*
pseudogating in, 602
"real-time," 602
respiratory synchronization in, 602
spatial localization of signal for, 587-588, *589-590*
spectroscopy and, 611
spin echo method, 592, *596, 868,* 868
time considerations in, 592-595
volume, *590,* 591-592, *595, 596*
with anisotropic voxels, 592, *596*
instrumentation for, *605-607,* 605-608
optimization of cardiovascular images on, 866-869, *868*
paramagnetic substances' effects on, 604, 605
phase display in, 870-871
pulse sequences for, 582-586, *583-585*
defined, 618
for measurement of T1 and T2, *585-586,* 585-586
inversion recovery, 583, *584*
partial saturation, 582-583, *583*
saturation recovery, 582-583, *583*
spin echo, 583-585, *584,* 592, *596,* 618
steady-state precession, 613
relaxation in, 576, 578-581, *581*
longitudinal mechanisms of, 580-581, *582*
transverse mechanisms of, 581
signal in, 576-578, *579-580*
detection of, 576, *579*
determinants of magnitude of, 577
processing of, 577, *579*
spatial localization of signal from, 586
by selective excitation, 588
frequency-dependent, 587, *589*
phase-dependent, 587, *590,* 590-591
spectroscopy with, 610-616
analysis of biological samples by, 612
analysis of pure compounds in solution by, 612
basis for, *610,* 610-611
carbon-13, 615
clinical cardiac, 873
evaluation of reaction kinetics with, 611-612
image selected in vivo (ISIS), 614
imaging and, 611
phosphorus-31, *614,* 614-615
potassium-39, 615-616
proton, 615
sodium-23, 615-616
spatial localization in, 612-614, *613*
technique of, 611-612
T1 and T2 relaxation times in, 576, 618
measurements of, *585-586,* 585-586
quantitative importance of, 578
techniques for, 581-586
width of spectra in, *611,* 611
Nucleosome(s), *15,* 15, 17
defined, 62
Nucleotide
defined, 62
Nucleus tractus solitarius
in cardiovascular regulation, 326-327
Nurse(s)
clinical specialist
home visits by, 2526
pediatric cardiology clinician
role in cardiac rehabilitation program, 2268
Nutation
defined, 617
Nutrition, 2354-2357. *See also* Diet
assessment of, 2356
requirements for, 2354
Nutritional disorder(s). *See also* Malnutrition; particular disorders
pharmacology of cardiac drugs in, 2363-2368
Nutritional therapy, 2356-2357
Nutritionist
role in cardiac rehabilitation program, 2268
Nyquist limit, *538,* 538

Obesity
atherosclerosis and, 1992
Obesity-hypoventilation syndrome
cor pulmonale due to, 2504
Oblique sinus of pericardium, 110
Obstetric management. *See* Labor and delivery; Pregnancy
Obstructive lesion(s). *See also* particular lesions
anatomic location of
clinical significance of, 1304-1305
assessment of severity of, 1305-1306
clinical physiology of, 1304t, 1304-1307
Obstructive pulmonary disease. *See under* Pulmonary disease
Obtuse margin of heart, 111
Ochre mutation
defined, 63
Oculoauriculovertebral dysplasia. *See* Goldenhar's syndrome
Ohm's law, 254, 302, 548, 2140
Okazaki fragment(s), 12, *13*
OKT3
for immunosuppression after cardiac transplantation, 2235
in rejection management, *2248-2249,* 2248-2249
Oligohexamer labeling, 21
Oligonucleotide(s)
defined, 63
synthesis of, 23
Oncocytic cardiomyopathy. *See* Ventricular tachycardia, incessant, in infants
Oncogene(s), 30-31
cellular, 31
expression of
during cardiac myogenesis, 31-32, *33*
viral, 30
Oncogenic virus(es), 30
Ondine's curse, 357, 2504
Open heart surgery. *See* Cardiac surgery
Open label study, 147
Opening snap
of mitral stenosis
innocent third heart sound vs., 1925
Operating room
temperature of, 2293
for neonate, 2481
Operator
defined, 63
Operon(s), 15-16
Optic neuropathy
ischemic
cardiac surgery and, 2312-2313
Orthodontic treatment, 2353
Orthopedic surgery
for paraplegia due to ischemic spinal cord injury, 2456
for spastic hemiplegia, 2454, 2455
Orthopedics, 2445-2461
complications of congenital heart disease involving, 2451-2456
congenital syndromes involving, 2456-2458
systemic disease involving, 2458-2460
Orthopnea
diagnosis of
in infant, 2008
Osborne wave
in hypothermia, 752, *753*
Oscillometry
blood pressure measurement by, 493, 681-682
Oscilloscope
cathode-ray
electrocardiograph using, 511-512, *513*
Osler, William, 1246
Osler's node(s)
in infective endocarditis, 1564, 2422
Osmolar clearance, 456
Osteoblastoma
embolization for, 992

Osteogenesis imperfecta
hematologic and oncologic problems with, 2329t
orthopedic problems in, 2459-2460
Osteomyelitis
rheumatic fever vs., 1497
sternal, *2464,* 2464
Osteosarcoma
intra-arterial chemotherapy for, 992
Ostium primum, 85, 1024
Ostium secundum, 85, 1025
Ototoxicity
of diuretics, 2017
of furosemide, 2103
Ouabain
inotropic effect of
sodium-calcium exchanger in, 205
Outlet chamber, 1248
Outlet foramen, 1249
Outlet ridge(s), 87
Outlet segment, 81
Outlet septum. *See under* Ventricular septum
Overdrive pacing. *See under* Pacing
Overdrive suppression, 313
Overload
actin changes in, 38-39
blood pool imaging in assessment of, 842-843
cardiac growth secondary to, 36-37
chronic
effects on liver, 2359-2360
isomyosin shifts in response to, 36-37, *37,* 219
Oversensing
in antitachycardia pacing, *2159,* 2159
Oxacillin, 2052
parenteral dosage for severe infection, 2057t
Oxidative phosphorylation, 196-197
Oximetry
causes of inaccurate readings in, 920-921, 925
defined, 919
in cardiac catheterization, 919-926
pulse, 2296
limitations of, 2483, 2485
Oxygen
alveolar pressure of
barometric pressure and, 442
arterial blood content of, 290
in newborn, 291
consumption of. *See* Oxygen consumption
myocardial. *See* Myocardial oxygen consumption
dissolved, 289
defined, 919
in oximetric calculations, 924-925
hemoglobin-bound, 290
high concentrations of
safety of, 2297
in metabolic regulation of myocardial blood flow, 258
in regulation of ductus arteriosus closure, 2109-2110
molecular
paramagnetic susceptibility of, 603
partial pressure of
barometric pressure and, 441-442
supplemental
effects on pulmonary circulation, 379
in congestive heart failure management, 2019-2020
in cor pulmonale management, 2504-2505
in postoperative care, 2253-2254
in ventricular septal defect management, 1014
pulmonary edema due to, *397,* 397
systemic delivery of
regulation of, 289-293
transfer of, across placenta, 282
Oxygen capacity
defined, 919
Oxygen cascade, 442
Oxygen consumption
cardiac output and, 832
defined, 927
in newborn, 291-292, *292*
maximum, 429
measurement of, in children, 432
measurement of, 930t
in cardiac catheterization, 927-929
in cardiac rehabilitation program, 2269
in exercise testing, *831,* 831, 833
myocardial. *See* Myocardial oxygen consumption
normal values for, 927
systemic, 290, *291*
tables for estimation of, 929, 930t
underestimation of, 928t, 928
formula for correction of, 928, 929t
Oxygen content
defined, 919
Oxygen dissociation curve
altitude's effects on, 443
oxygen saturation calculation from, *920,* 920
Oxygen extraction
in response to exercise, 430
myocardial
baseline, 246
systemic
in compensation of congestive cardiac failure, 246
Oxygen extraction ratio (OER), 293
Oxygen free radical(s)
in postischemic dysfunction, 274-275, *275*
in reperfusion injury, 269-270
Oxygen paradox, 268-269
Oxygen saturation
calculation of
in presence of shunt, 921
methods for, *920,* 920-921
causes of abnormal values of, 925
defined, 919
normal values for, 925t
Oxygen transport
changes in
with altitude, 442-443, 443t
in newborn, 291-292, *292*
monitoring of, 292-293
systemic, 289-291
Oxygen-15
positron emission tomography using, 620, 875
Oxygenation
monitoring of, during anesthesia, 2296
transcutaneous monitoring of
limitations of, 2483, 2485
Oxygenator(s)
for cardiopulmonary bypass, 2299-2300
priming for, 2300-2301
Oxygen-hemoglobin dissociation curve. *See* Oxygen dissociation curve
Oxytocin
effects on pulmonary circulation, 374t, 377
Oxytocin challenge test, 2391-2392, 2392t

P cell(s)
of sinus node, 122
P value, 647-648
P wave(s), 715-716, *716-717*
himalayan
in Ebstein's anomaly, 1137
T wave vs., 722, *723*
U wave vs., 722
Pacemaker
wandering, 1954
Pacemaker(s) (artificial). *See also* Pacing
activity-detecting rate-variable
for sinus node dysfunction, 1780
antitachycardia
implantation techniques for, *2158,* 2158-2159
noninvasive electrophysiology studies with, *2160,* 2160
batteries for, 2141-2142
circuitry for, 2142-2143
components of, 2141-2143, *2143*
connectors for, 2143
countershock with, 2170
endocardial
epicardial vs., 2146
environmental hazards to, 2148
epicardial, *2146*
endocardial vs., 2146
failure of
syncope due to, 1937, *1939*
followup with, 2147-2150, *2148*
housing of, 2141
noninvasive clinic evaluation of, 2148-2150
nuclear magnetic resonance and, 873-874
operation of, 2139-2144
pocket infection, 2464
programmability of, *2143,* 2143
programming of, 2149
sensing by, 2140-2141, *2142*
tachycardia mediated by, 2153
telemetry with. *See* Telemetry
timing cycles of, *2144,* 2144
Pacemaker cell(s)
automaticity of, 298-299, *299*
latent, 313
Pacemaker dependence
defined, 2149
testing for, 2149
Pacemaker recovery time, 1766, *1767*
Pacemaker syndrome, 1912, 2145
defined, 2153
Pacing. *See also* Pacemaker(s)
age-related heart rate criteria for, 2136-2137, 2137t
antitachycardia, 2156-2161
complications with, 2160
direct-current cardioversion vs., 2164-2165
electrophysiology of, *2158-2160,* 2159-2160
for ventricular arrhythmias, 1900
modes for, 2156-2157, *2157-2158,* 2166-2167
patient selection for, 2157
preoperative electrophysiologic studies for, 2157-2158
self-monitoring telemetry with, *2160,* 2160
tachycardia termination protocol for, 2159-2160
transesophageal, 2164, *2165*
asynchronous
defined, 2152
atrial demand (AAI)
indications for, 2147
atrial synchronous (VDD), 2145
atrioventricular synchronous (DVI), 2144-2145
atrioventricular synchrony in, 2145

Pacing (cont.)
atrioventricular universal (DDD)
indications for, 2147
bipolar, 2140, *2141*
defined, 2152-2153
unipolar vs., 2146
burst, 2166
choices of system for children, 2146-2147
competitive underdrive, 2166
demand
defined, 2153
electrical principles of, 2139-2140
for atrial flutter, 1858, *1860*
for bradycardia, 2135-2155
for sudden death prevention, 1912
for cardiopulmonary arrest, 422
for congenital complete atrioventricular block, 1805-1806
for sinus node dysfunction, 1778-1779, *1779*, 1780
for surgical complete atrioventricular block, 1807
glossary of, 2152-2154
indications for, 2135-2139, *2136*
inhibited mode
defined, 2153
leads for, 2147, *2148*, 2152, 2153
lower rate in, defined, 2153
overdrive, 2166
for atrial flutter, 1857-1858, *1859*
for atrial tachycardia, 2167
for supraventricular tachycardia, *1822*, 1823
for ventricular tachycardia, 1897
mechanism of, 313
oversensing in, 2141
defined, 2153
paired
for supraventricular tachycardia, 1823
parameters in
defined, 2153
physiologic, 2144-2146
choice of device for, 2147
defined, 2153
programmed extrastimulation, 2166
rate responsiveness in, 2145
results with, 2150-2151, *2151-2152*, 2152t
sensing in, 2140-2141, *2142*
strength-duration curve in, 2140, *2141*, 2149
terminology of, 2139, *2140*
threshold for, 2140, *2141*
transesophageal, 2164t, 2164-2167, *2165*
in myocardial infarction management, 1718
in supraventricular tachycardia management, 1822
transthoracic
for bradyarrhythmias, 2171-2172
undersensing in, 2141
unipolar, 2139-2140, *2141*
bipolar vs., 2146
defined, 2154
upper rate in
defined, 2154
ventricular demand (VVI)
indications for, 2147
Pain. *See also* Chest pain
cutaneous, 1947
features of, 1947
in myocardial infarction, 1697
management of, 1717
musculoskeletal, 1947
types of, 1947
visceral, 1947
Pair production, 562-563, *563*
Palindrome
defined, 63
Pallor, 674
Palmar crease
single
syndromes associated with, 678t, 678
Palmitate
myocardial metabolism of, in ischemia
positron emission tomography studies of, 622-623, 875-876
Palpation
blood pressure measurement by, 681
in cardiac physical examination, 683-684
of heart sounds, 684
Palpitation(s), 1726
diagnosis of
with transesophageal pacing, 2166
Pancreas
involvement of
in acute myocardial infarction, 1695
Pancreatitis
acute
pain in, 1949
electrocardiographic findings in
myocardial infarction vs., 1715
Pancuronium (Pavulon), 2295t, 2553t
for induction and intubation, 2297
in respiratory care of neonate, 2483
Panic disorder, 337
mitral valve prolapse and, 1978
Papaverine
effects on pulmonary circulation, 374t, 378
Papillary muscle(s)
in atrioventricular canal defects, 1040
echocardiographic examination of, 1044
left ventricular, 117, 118
right ventricular, 114, *115-116*
rupture of
after myocardial infarction, 2283
Papillary muscle infarction, 1686, 1700
electrocardiographic findings in, 746, 1706-1707, 1708t
Paraamino hippurate (PAH)
in renal plasma flow measurement, 451
renal handling of
in neonate, 465
Parachute mitral valve, 1312
iatrogenic, 1040, 1044
Paralytic agent(s), 2553t
Paramagnetic
defined, 617
Paramagnetic agent(s)
enhancement of nuclear magnetic resonance contrast with, 872-873
Paramagnetic susceptibility, 603
Paramagnetism, *603*, 603
effects of
on nuclear magnetic resonance images, 605
on nuclear magnetic resonance relaxation, 604
Paraplegia
after coarctation repair, 2033
due to ischemic spinal cord injury
management of, 2455-2456
Parasitic infection(s)
cardiac manifestations of, 2471-2472
Parasympathetic agonist(s)
effects on pulmonary circulation, 374t, 376
Parasympathetic antagonist(s)
effects on pulmonary circulation, 374t, 376
Parasympathetic blockade
in parasympathetic neuronal function evaluation, 335
Parasympathetic neuronal function
evaluation of, 335
Parasystole
diagnosis of, 1871-1872, *1872*
in otherwise normal heart, 1887
mechanisms of, *316*, 316-317
Parchment right ventricle, 1893
Parent(s)
of newborn with congenital heart disease
psychological considerations, 2520-2521
reaction to fetus with congenital heart disease, 2519-2520
Parenteral nutrition, 2356
Parietal band(s), 115-116, *116*
in double-outlet right ventricle, 1214, *1214*
Paris nomenclature, 177-178
Paroxysmal dyspnea. *See* Tetralogy spell(s)
Paroxysmal hypoxemic spell(s). *See* Tetralogy spell(s)
Paroxysmal tachycardia
atrial
postoperative, 2258
supraventricular
in pregnancy, 2381
ventricular
in infants, 1884
Partial anomalous pulmonary venous connection. *See under* Anomalous pulmonary venous connection(s)
Partial saturation
defined, 617
Partial volume effect
in computed tomography, 631
in nuclear magnetic resonance imaging, 609
in positron emission tomography, 620
Pasteur effect, 193
Patau syndrome. *See* Trisomy 13
Patent ductus arteriosus, 1055-1069
altitude and, 446-447
anatomy of, 1057, *1057-1060*
aneurysm of, 1063
after surgical ligation, 2027
angiographic assessment of, 957t, 1063-1064
antenatal steroids' effects on, 2118
atrioventricular canal defect with, 1044-1045
bilateral, 1057, *1059*
clinical features of, 1060-1062, 2487
coarctation of aorta with, 1060, 1067
complex lesions associated with, 1066-1067
complications of, 1062-1063
congestive heart failure due to, 2012
definitive diagnosis of, 1063-1064
differential diagnosis of, 1064-1066
Doppler assessment of, 790, *792*
echocardiographic findings in, *776*, 776, *1062*, 1062
electrocardiographic findings in, *743*, 744, 1062
etiology of, 1056
furosemide therapy and, 2101-2102, 2113
in premature infant
clinical factors increasing incidence of, 2113
clinical problem of, 2112-2113
reasons for, 2113
treatment of, 1964-1965, 2114-2118
incidence of, 1055-1056
"intermittent", 1059, *1061*
lesions dependent on, 1067
management and therapy of, 1067-1068, *1068*. *See also* Patent ductus arteriosus, surgical treatment of

in neonate, 2486-2488
in premature infant, 1964-1965, 2114-2118
optimal time for closure, 2114
presenting at 4-12 months, 1968
with occluding device, *1068,* 1068, 2202-2205, *2204-2207*
murmur of, 689, 1060-1061
mammary souffle vs., 1926
venous hum vs., 1064, 1926
nature of left-to-right shunt in, 1058-1060
physiology of, 1057-1060
pregnancy with, 2379
radiographic findings in, 697, *701,* 1062
recurrence of, after closure, 2117
reversed, 1060
right, 1057, *1059*
risk for recurrence in subsequent child, 176t
surgical treatment of, 1067-1068, 2026, 2488
complications of, 2026-2027
patient selection for, 2027-2028
persistent patency or recanalization after, 2026
residua of, 2026
systemic hypertension after, 1994
transposition of the great arteries with, 1060, 1178, 1180-1181
volume changes with, 1058
"window", 1057, *1058*
Pavulon. *See* Pancuronium
Pectinate muscle(s)
of left atrium, 117
of right atrium, 113
Pectus excavatum
chest radiographic findings in, 694
electrocardiographic findings in, 726-727
Pedigree chart, 171-172, *172*
Pelvis
angiography of, 988-993
neoplasms of
angiography in management of, 992
trauma to
angiography in assessment of, 988-992, *991*
vascular supply to, 988, *990*
Penetrance
defined, 174
Penicillin(s), 2051-2053. *See also* particular penicillins
adverse effects of, 2052
allergy to, 2049
skin testing for, 2052
dosage adjustment for renal insufficiency, 2440t
extended-spectrum, 2053
adverse effects of, 2053
aminoglycoside synergism with, 2056
for brain abscess, 2467
for infective endocarditis, 1571-1572
for Lyme disease, 1538-1539
for rheumatic fever prophylaxis, 1498-1499
penicillinase-resistant, 2052
adverse effects of, 2052
phenoxymethyl (penicillin V potassium), 2051-2052
resistance to, 2051
structure of, *2051*
Penicillin G, 2051-2052
dosage adjustment for renal insufficiency, 2440t
parenteral dosage for severe infection, 2057t
toxicity of, 2049
Penicillin V potassium, 2051-2052
Penta X syndrome, 2429t
Pentobarbital
dosage adjustment for renal insufficiency, 2440t
Peptide hormone(s)
kidney in degradation of, 463
Percussion
in cardiac physical examination, 684
Percutaneous transluminal coronary angioplasty. *See* Balloon angioplasty, coronary
Perfusion. *See* Blood flow
matching ventilation to. *See* Ventilation/perfusion matching
myocardial. *See* Myocardial perfusion
Perfusion imaging
myocardial. *See also under* Myocardial scintigraphy
by digital subtraction angiography, 907-908
by positron emission tomography, 875
vascular, 847, *848*
Perfusion pressure
coronary vascular reserve and, 260
defined, 256
myocardial blood flow and, 256
Periadenitis mucosa necrotica recurrens, 2418
Pericardial abscess
computed tomography assessment of, *889*
Pericardial cavity, 110
Pericardial cyst
computed tomography assessment of, *889*
Pericardial effusion(s)
computed tomography assessment of, 883, *889*
nuclear magnetic resonance imaging in, 863, *864*
postoperative, 1601-1602
Pericardial fluid, 110, 1590
intrapericardial pressure and, 1592
Pericardial friction rub
in pericarditis, 1592
Pericardial window surgery, 1596-1597
Pericardiocentesis
complications of, 1596
diagnostic, 1596
Pericardiosternal ligament(s), 110
Pericarditis, 1590-1599
clinical manifestations of, 1592, *1593-1595*
constrictive, 1598
computed tomography assessment of, *888*
hematologic complications of, 2342
in chronic renal failure, 2433
nuclear magnetic resonance imaging in, 863
restrictive cardiomyopathy vs., 1636
with purulent pericarditis, 1597
diagnosis of, 1593-1596, *1595*
differential diagnosis of, 1596
early repolarization syndrome vs., 742
echocardiographic findings in, *1595,* 1595
electrocardiographic findings in, 744-745, *745,* 1593-1595
myocardial infarction vs., 745, 1715
epidemiology of, 1590-1591
etiology of, 1591-1592
in chronic renal failure, 2432-2433
in connective-tissue disease, 754
in juvenile rheumatoid arthritis, 1528-1529
in Kawasaki disease, 1554
in systemic lupus erythematosus, 1530, 1530-1531
incidence of, 1590-1591
laboratory evaluation of, 1593-1596
myocarditis vs., 1585
pathology and pathogenesis of, 1592
prognosis in, 1597
purulent
diagnosis of, 1596
prognosis in, 1597
treatment of, 1596-1597
radionuclide imaging in assessment of, 848
rheumatic, 1490, *1491,* 1493
treatment of, 1596-1597
viral, 1598
rheumatic fever vs., 1498
Pericardium
anatomy of, 110, 1590
disease of
chest pain due to, 1949
computed tomography assessment of, 883, *888-889*
nuclear magnetic resonance imaging of, 863
function of, 1590
histologic features of, 110
parietal, 110, 1590
histologic features of, 110
trauma to
blunt, 2537
penetrating, 2538
tumors of, 2338
visceral, 110, 1590
histologic features of, 110
Pericyte(s)
in pulmonary arteries, 361
Perimicrovascular hydrostatic pressure
decreased
pulmonary edema due to, *396,* 396
pulmonary fluid balance and, 390
Perimicrovascular oncotic pressure
pulmonary fluid balance and, 390-391
Perimyocarditis, 1585
Period (ultrasound)
defined, *526,* 526
Periodic wake phenomenon, 1920
Periodontosis, 2404t
Peripartum cardiomyopathy, 2378
Peripheral vascular disease
with coronary artery disease, 2284
Peripheral vascular system
development of
in space, *438,* 438
Peritoneal dialysis, 2438t, 2438. *See also* Dialysis
for postoperative renal failure, 2262
Peritonitis
electrocardiographic findings in, 754
Peroxisome(s), 1668
Persantine. *See* Dipyridamole
Persistent atrioventricular ostium. *See* Atrioventricular canal defect(s)
Persistent ostium primum defect
in atrioventricular canal defects, 1037
Persistent pulmonary hypertension of newborn, 364
with congenital heart disease, 2484-2485
without congenital heart disease, 2485-2486
Pertussis toxin
effects on adenyl cyclase activity, 322
Phage
defined, 60
Pharmacokinetics
two-compartment model of, *468,* 468-469
Pharmacology, 468-474. *See also* particular drugs
Phase
defined, 617
Phase encoding
blood flow measurement using, 602
defined, 617
spatial localization of nuclear magnetic resonance signal using, 587, *590*
Phase interference phenomenon, 599, *600*
Phenergan. *See* Promethazine

Phenobarbital
dosage adjustment for renal insufficiency, 2440t
Phenothiazine(s)
effects on electrocardiogram, 751
hypoadrenergic dysautonomia due to, 340
Phenotype
defined, 63
Phenprocoumon
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2367
Phentolamine (Regitine), 2549t
effects on pulmonary circulation, 373, 374t, 375
for heart failure after cardiac surgery, 2095
pharmacology of, 2088t, 2090
Phenylbutazone
myocarditis and, 1582
Phenylephrine (Neosynephrine)
alpha-adrenergic receptor responsiveness evaluation using, 334
as antiarrhythmic agent, 2133-2134
effects on pulmonary circulation, 373, 374t
in cardiopulmonary resuscitation, 411-412
in supraventricular tachycardia treatment, 1822-1823
in syncope diagnosis, 1944-1945
Phenytoin (diphenylhydantoin; Dilantin), 2127t, 2129-2130, 2550t
dosage adjustment for renal insufficiency, 2441t
effects on electrocardiogram, 751
for digitalis intoxication, 1897
for ventricular arrhythmias, 1895, 1898-1899
prophylactic use of
in brain abscess treatment, 2467
use of, in pregnancy, 2385, 2386t
congenital heart disease and, 676t, 678t
Pheochromocytoma, 2494
electrocardiographic findings in, 754
hyperadrenergic dysautonomia due to, 338
Phlebectasia
congenital, *2423*, 2423
Phlebotomy
for hyperviscosity syndrome, 1999
to reduce red cell volume for cardiopulmonary bypass, 2301
Phocomelia
congenital heart disease with, 678t, 678-679
Phosphate. *See also* Hyperphosphatemia; Hypophosphatemia
inorganic
in cardiac muscle, nuclear magnetic resonance studies of, *614*, 614-615
tubular transport of, 454
Phosphate buffer system, 461
Phosphocreatinine
in cardiac muscle
nuclear magnetic resonance studies of, *614*, 614-615
Phosphodiesterase inhibitor(s)
mechanisms of action of, 2068
Phosphofructokinase
activation of
in ischemic myocardium, 1689
in glycolysis, 193
Phospholamban, 41, 206t, 207
sarcoplasmic reticulum content of
during development, 209
Phospholipid(s), 475, *476*
Phosphorus
cardiotoxicity of, 1674
Phosphorus-31
nuclear magnetic resonance spectroscopy using, *614*, 614-615
Phosphorus/oxygen ratio, 197
Phosphorylase
in glycogenolysis, 192
Phosphorylase kinase deficiency
cardiac, 1665-1666
Photoelectric effect, *562*, 562
Photoelectric plethysmography
blood flow measurement using, 498
Photoelectron(s), 556, *562*, 562
Photomultiplier
in positron emission tomography, 624
Photomultiplier tube(s)
for gamma cameras, *567*, 567
Photon(s), 552-553, 560
annihilation
defined, 623
defined, 624
interactions of, with matter, *562-563*, 562-563
Photosensitivity
in systemic lupus erythematosus, 1530
Phototherapy
in premature infants
patent ductus arteriosus and, 2113
Phrenic nerve
injury to
diagnosis of, 2512
diaphragmatic paralysis due to, 2511-2512
in coarctation repair, 1370
in open heart surgery, 2253
in surgical ligation of patent ductus arteriosus, 2026-2027, *2027*
mechanics of infant ventilation with, 352
recovery of function after, 2512
Physical education teacher
role in cardiac rehabilitation program, 2268
Physical examination, 679-683
cardiac, 683-689
in evaluation of autonomic control of cardiovascular function, 331
Physostigmine (Antilirium)
in obstetric management, 2389
Phytanic acid storage disease, 1668
Pickwickian syndrome, 2504
Picture archiving and communications system(s) (PACS), 663
Piezoelectric
defined, 525
Pindolol
pharmacology of, 2364t
Pink tetralogy. *See* Tetralogy of Fallot, acyanotic
Pinocytotic vesicle(s)
of alveolar septum capillaries, *387*, 387
Piperacillin, 2053
aminoglycoside synergism with, 2056
dosage adjustment for renal insufficiency, 2440t
parenteral dosage for severe infection, 2057t
Pitressin. *See* Antidiuretic hormone
Pituitary gland, 2495
disease of, 2495
Pituitary insufficiency, 2495t, 2495
Pixel(s)
defined, 617, 630, 852
Placebo
in randomized clinical trial, 147
Placenta
anatomy of, 280, *281*
blood flow in
echocardiographic assessment of, 822-823
fetal, 281
fetal regulation of, 281-282
maternal, 280-281
maternal regulation of, 281
function of, 282-283
oxygen consumption by, 282
oxygen transfer across, 282
vascular resistance in, 281
echocardiographic assessment of, 822-823
gestational age and, 282
Plasma osmolality
estimation of, 459
Plasmapheresis
in rheumatic fever management, 1500
Plasmid(s), 24
defined, 63
Platelet(s)
altitude's effects on, 444
functional defects of
after cardiopulmonary bypass, 2344
reduced lifespan of, in polycythemia with hypoxemia, 1999
storage of, in lungs, 365
surgical bleeding due to disorders of, 2343
drugs causing, 2343t
Platelet-derived growth factor (PDGF), 485
endothelial synthesis of, 486
Play therapy
in preparation for medical procedures, 2522
Pleiotropy
defined, 174
Plethysmography
impedance
blood flow measurement using, 497, 498
photoelectric
blood flow measurement using, 498
Pleural effusion, *2025*
chest pain due to, 1948
drainage of, *2025*
transudative, 2514
Pleurisy
chest pain due to, 1948
in rheumatic fever, 1491
in systemic lupus erythematosus, 1530
Pleurodesis
for chylothorax, 2514
for persistent pleural effusion, 2514
Pleurodynia, 1948
Pleuroperitoneal shunt
for chylothorax, 2514
for persistent pleural effusion, 2514
Plotter(s)
computer, 660
Plumbicon tube(s), 555, 639
Plumbism, 1674
Plus-minus method, 9
Pneumococcal infection
culture techniques in, 2047
endocarditis due to, 1569
pericarditis due to, 1591
vaccine for, for asplenic children, 2473
Pneumocystis carinii infection
after heart transplantation, 2245, 2468
in acquired immune deficiency syndrome, 1609
Pneumocyte(s)
of alveolar septum, 387-388
Pneumomediastinum
after surgical ligation of patent ductus arteriosus, 2027
electrocardiographic findings in, 727
Pneumonectomy
electrocardiographic changes after, 727
Pneumonia. *See also* Pneumonitis
after heart transplantation, 2468

electrocardiographic findings in
myocardial infarction vs., 1715
in acquired immune deficiency syndrome, 1609
in rheumatic fever, 1494
pericarditis and, 1591
Pneumonitis. *See also* Pneumonia
in acquired immune deficiency syndrome, 1608-1609
in rheumatic fever, 1491
Pneumotachygraph
for automated exercise testing, *831,* 831
Pneumotaxic center, 357
Pneumothorax, *2025*
after surgical ligation of patent ductus arteriosus, 2027
chest pain due to, 1948
electrocardiographic findings in, 727
myocardial infarction vs., 1714
Point of maximum impulse, 683
Poiseuille's law, 930-931
Poisson's formula, 502
Polarographic method
for oxygen consumption measurement, 928-929
Policy
defined, 546
Polyadenylation
defined, 63
Polyarteritis nodosa, 986-987, *987*
infantile
Kawasaki disease and, 1546
Polyarthritis
bacterial
rheumatic fever vs., 1497
Polycythemia, 2336-2337, 2337t
altitude and, 443-444
brain abscess and, 2308
cardiac catheterization with, 962-963
clinical manifestations of, 1998-1999
coronary vascular reserve in, 261-262
cyanosis and, 672
genetic forms of, 2337
headache in, 676
in development of cor pulmonale, 2502
in hypoxemia, 1998-1999
in Monge's disease, 446
in tetralogy of Fallot
medical management of, 1089
in transposition of the great arteries, 1201
intestinal ischemia and, 2359
myocardial infarction in, 1714
neonatal, 2336-2337
defined, 2336
primary, 2337
relative, 2337
secondary, 2337t, 2337
spurious, 2337
stress, 2337
Polycythemia vera, 2337
Polydactyly
syndromes associated with, 678t, 678
Polymerase chain reaction (PCR), 25-27, *26-27*
Polymorphism information content (PIC), 28
Polymyxin B
in septic shock management, 2471
Polynucleotide(s)
synthesis of, 23
Polyploidy, 176
in human heart, 165
Polysplenia syndrome (left isomerism), 695, 1295-1296, 1297-1298, 2405-2406
atrioventricular canal defects in, 1045
cardiovascular abnormalities associated with, 1293t, 1296
clinical features of, *1294-1297,* 1295-1296
defined, 1288
echocardiographic assessment of, 769
in fetus, 807, *808*
immunization recommendations for, 2473
incidence, etiology and genetics of, 1288-1289
management and prognosis in, 1296
pulmonary venous connection in, 1156
renal abnormalities in, 2430t
Polyvinyl alcohol foam (Ivalon)
embolization using, 974, 1479t
Pompe's disease, *1664-1665,* 1664-1665, 2406
congestive heart failure due to, 2013
endocardial fibroelastosis vs., 1626
gene therapy for, 59
molecular basis of, 54
Popliteal artery entrapment syndrome, 988, *990*
Population, 142-144
characteristics of, 142
defined, 141
Pore(s) of Kohn, 350
Porstmann technique
for ductal occlusion, 1068, 2202
Portal hypertension, 981, *984*
Positive end-expiratory pressure (PEEP)
for neonate, 2483
in postoperative care, 2254
physiologic
for infants, 352
Positron
defined, 624
Positron emission, 561
Positron emission tomography (PET), 619-624
advantages of, over other radionuclide techniques, 623
basic principles of, *619,* 619-620
blood flow evaluation with, 497, 621-622
tracer kinetics in, 621
cardiac metabolic studies with, 622-623
clinical aspects of, 874-876
determination of tracer concentration with, 620-621
drug-labeling with, 876
glossary of terms, 623-624
history of, 619
in myocardial infarction diagnosis, 1711
instrumentation for, 620
technical considerations affecting cardiac studies with, 620
tracers used in
for cardiac studies, 620-621
metabolic, 622
Postcoarctectomy syndrome, 1370, 1993-1994, 2263
intestinal ischemia in, 2359
Postembolization syndrome, 978
Posterior fascicular block. *See* Left posterior hemiblock
Postischemic dysfunction, 266, 273-275, *275*
Postmaturity
placental blood flow in, 281
Postoperative care, 2251-2266. *See also* particular procedures and under particular disorders
airway and breathing, 2251-2255
cardiovascular system, *2095,* 2095, 2255-2258
central nervous system, 2258-2259
fluids and electrolytes, 2259
gastrointestinal system, 2259-2260
hematology, 2260-2261
infection, 2261
kidneys, 2261-2262
normal chest roentgenogram findings in, 2252
routine orders for, *2252,* 2556
systematic approach to, 2251-2262
Postoperative inflammatory syndrome(s), 1600-1604. *See also* Postperfusion syndrome; Postpericardiotomy syndrome
Postpartum period
cardiomyopathy in, 2378
hemodynamics of, 2375-2376
Postperfusion pulmonary congestion syndrome, 2253
Postperfusion syndrome, 1603
hematologic complications of, 2342
Postpericardiotomy syndrome, 1600-1603, 2264
after cardiac trauma, 2537, 2538
after surgical repair of atrial septal defect, 2028-2029
diagnosis of, 1601-1602
etiology and pathogenesis of, 1600-1601
incidence of, 1600
postperfusion syndrome vs., 2342
radiographic findings in, 711
treatment of, 1602-1603
Posttranslational modification
defined, 63
Potassium. *See also* Hyperkalemia; Hypokalemia
in diabetic ketoacidosis management, 2495
in metabolic regulation of myocardial blood flow, 258
intracellular
nuclear magnetic resonance studies of, 616
radiolabeled
blood flow measurement using, 495
regulation of
in renal failure management, 2437
renal excretion of
in neonate, 465
resting membrane potential and, 294-295, *295*
tubular transport of, 454
Potassium channel(s), 306-307, *306-307*
Potassium chloride, 2553t
Potassium-39
nuclear magnetic resonance spectroscopy using, 615-616
Potts anastomosis, 2211
for single ventricle, 1268-1270
for tetralogy of Fallot, 1091-1092
sequelae of corrective surgery after, 2037
nuclear magnetic resonance imaging of, 860, *861*
Power
of research study, 149
P-R interval
on electrocardiogram, 716, *718*
short
causes of, 740
P-R segment
on electrocardiogram, 716-717
Practice
recommended
defined, 546
Practolol
effects on pulmonary circulation, 374t, 375
Prazosin (Minipress), 2434t, 2549t
effects on pulmonary circulation, 373, 374t, 375
for congestive heart failure, 2019, 2020t
for dilated cardiomyopathy, 1623, 2092
pharmacology of, 2088t, 2089, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2367

Prealbumin
in nutritional assessment, 2356
Precardiac cell(s)
origin and migration of, 153, *155*
Precession, *574-575,* 574-575
defined, 617-618
phase in, 576, *578*
Precordial catch, 675, 1948
Precordial thump, 421
Predictive value
negative, *143,* 143-144
positive, *143,* 143-144
Prednisolone, 2496, 2497t
Prednisone, 2496, 2497t
for Lyme disease, 1539
Preejection period/left ventricular ejection time ratio
in myocardial infarction, 1708-1709
Preexcitation, 738-740. *See also* Lown-Ganong-Levine syndrome; Mahaim fiber(s); Wolff-Parkinson-White syndrome
inheritance patterns of syndromes of, 55
Pregnancy, 2374-2396
after cardiac surgery, 2382
anticoagulation during, 2080, 2381-2382
arrhythmias during, 2381-2382
atrial septal defect and, 1028
cardiac disease in, 2377-2381
cardiac signs and symptoms in, 2376t, 2376-2377
cardiac surgery during, 2387
cardiovascular drug use during, 2384-2387, 2385t-2387t
cardiovascular evaluation during, 2377
coarctation of the aorta and, 1367, 1373
congenital heart disease complicating, 2378-2380
coronary artery disease and, 2383
counseling on risk of, 2383t, 2383-2384
endocarditis prophylaxis during, 2388
fears about, 2525
fetal assessment during, 2390-2393
indications for, 2390t
hemodynamic changes of, 2374t, 2374-2375
history of
in clinical assessment of heart disease, 676t, 676
in genetic evaluation, 172
Marfan syndrome and, 2399
medical management of cardiac patients during, 2384t, 2384
mitral valve prolapse and, 1983
myocardial infarction in, 1714
noninvasive diagnostic findings in, 2376t, 2377
nuclear magnetic resonance and, 874
prosthetic valves and, 1314, 2382
venous disease in, 2383
ventricular septal defect and, 1017
Preload, 224
atrial contraction and, 233
end-diastolic pressure as measure of, 233
estimation of, 224
force development and, *224,* 224
in intact heart, 232-234
in pump function regulation, 234
postoperative
adjustment of, 2255-2256
assessment of, 2255
stroke volume and, 237, *238*
studies from isolated cardiac muscle, 231, *232*
Preload reserve, 234
in fetal and newborn ventricle, *240,* 240
Premature atrial contraction(s), 1956
blocked, 1956
irregular sinus rhythm vs., 1953, *1954*
fetal, 815, *1906,* 1907
echocardiographic diagnosis of, 812, *814,* 814-815, *816*
sinoatrial exit block vs., 1758-1759
with aberrant ventricular conduction
premature ventricular contractions vs., 1865-1867, *1867-1869*
Premature junctional contraction(s)
blocked
irregular sinus rhythm vs., 1953
with aberration
premature ventricular contractions vs., 1867
Premature ventricular contraction(s), 1957-1958
clinical situations associated with, 1881-1896
acute, 1881-1883
coupling interval of, *1871-1872,* 1871-1872
differential diagnosis of, 1865-1869, *1867-1870*
electrocardiographic characteristics of, 1864-1874, *1865-1867*
exercise electrocardiography in assessment of, 1739-1740, *1740,* 1740t
fetal, 815, 1907
echocardiographic diagnosis of, 812-813, 815, *816-817*
frequent
defined, 1879
in children with otherwise normal heart, 1885-1887
in infants, 1884
in unoperated congenital heart disease, 1891-1892
in unoperated mitral valve prolapse, 1891
multiform vs. uniform, 1869, *1871*
noninvasive evaluation of, 1876-1879
postoperative, 2258
treatment of
acute, 1896-1897
with myocardial infarction, 1715
management of, 1718
Premedication
for cardiac catheterization, 948
for surgery, 2290-2291
Prenatal diagnosis. *See under* Diagnosis
Prerenal azotemia
diagnosis of, 2435t, 2435
Pressure. *See also* Blood pressure; Pressure-volume loop(s)
aortic valve gradients
errors in measurement of, 944
estimation of, 941, *941-942*
atrial. *See also* Left atrial pressure
right, 918
cardiac catheterization data, 915-919
normal, 916t
procedure for collection of, 915-916
defined, 232
Doppler estimation of gradients, 796-799, *798*
pulmonary artery. *See* Pulmonary artery pressure
ventricular. *See also* Left ventricular pressure; Right ventricular pressure
end-diastolic, as measure of preload, 233
end-diastolic volume and, 232, *233*
Pressure half-time
mitral valve area assessment using, 799
Pressure overload
blood pool imaging in evaluation of, 842-843
chronic
effects of, on liver, 2359-2360
Pressure-volume loop(s), 237-239, *237-239*
from equilibrium blood pool imaging, 839
from first-pass blood pool imaging, 841
Prevalence
in diagnostic test evaluation, *143,* 143-144
Preventive cardiology, 1987-1995
communication and education in, 1988-1989
concept of risk factors in, 1989
Primary fold, 81, 86
Primary foramen, 81, 86, *88*
Primary groove, 81
Primary ring, 104
Primary septum
formation of, 86-87, *89*
Primary transcript
defined, 63
Primaxin. *See* Imipenem
Primitive groove. *See* Primitive streak
Primitive node, 73
Primitive streak, 73, 152-153, *155*
Primitive ventricle, 80-81
Primitive yolk sac, 72
Printer(s)
computer, 660
Prinzmetal's angina, 1713, 2283-2284
Priscoline. *See* Tolazoline
Proarrhythmia, 2126
with class IC antiarrhythmic agents, 2131
Proband
defined, 171
Procainamide, 2127t, 2128, 2550t
adverse effects of, 2128
cimetidine interaction with, 2367
dosage adjustment for renal insufficiency, 2441t
effects on electrocardiogram, 750-751, *751*
for atrial fibrillation, 1861
for ventricular arrhythmias, 1898
pharmacokinetics of, 2128, 2364t
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2365
systemic lupus erythematosus and, 1532-1533
toxicity of
in renal failure, 471
use of, in pregnancy, 2385, 2386t
Procaine
effects on pulmonary circulation, 374t, 378
Procardia. *See* Nifedipine
Procedure
defined, 546
Progeria, 1678, 2416-2417
atherosclerosis in, 1993
Program(s). *See also* Software
defined, 658
Programming language(s), 661-662
Progressive scanning, 640
Projection reconstruction
planar nuclear magnetic resonance imaging using, 591, *594*
Prolapsing mitral leaflet syndrome. *See* Mitral valve prolapse
Prolonged Q-T interval syndrome. *See* Long Q-T syndrome(s)
Promethazine (Phenergan), 2553t
for obstetric analgesia, 2387t, 2389
premedication with
for cardiac catheterization, 948
Promoter sequence(s), 16
defined, 63
Propafenone, 2551t
Propiomazine (Largon)
for obstetric analgesia, 2387t, 2389
Proportion(s)

comparison of, 653
Propositus(-a)
defined, 171
Propranolol (Inderal), 2127t, 2131-2132, 2434t, 2551t
adverse effects of, 2131-2132
cimetidine interaction with, 2367
congestive heart failure due to, 675
dosage adjustment for renal insufficiency, 2440t
drug interactions with, 2131-2132, 2367
effects of
on electrocardiogram, 751
on pulmonary circulation, 374t, 375
for atrial flutter, 1857
for hyperthyroidism, 2492
for hypertrophic cardiomyopathy, 1633
for mitral valve prolapse, 1983
for paroxysmal hypoxemic spell, 1090
for supraventricular tachycardia, 1823, 1824-1825
for ventricular arrhythmias, 1899
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2365
use of, in pregnancy, 2386t
Propylthiouracil (PTU)
for hyperthyroidism. 2492
Prostacyclin, 366
effects of
antiplatelet, 2081
on pulmonary circulation, 374t, 377
renal, 464
endothelial production of, 366, 486
in response to hypoxic pulmonary vasoconstriction, 370
shear stress and, 372, 484
in regulation of ductus arteriosus closure, 2111-2112
postnatal drop in pulmonary vascular resistance and, 363
renal handling of sodium and, 458
renal production of, 464
Prostaglandin(s)
effects of
antiplatelet, 2081
on pulmonary circulation, 374t, 377
on renal blood flow, 451
in regulation of ductus arteriosus closure, 2110-2112
in response to hypoxic pulmonary vasoconstriction, 370
inactivation of, in lungs, 366
postnatal drop in pulmonary vascular resistance and, 363-364
renal, 464
in response to congestive heart failure, 2426
renal handling of sodium and, 458
therapy with, in congenital heart disease, 1961, 2118-2121, 2552t
in pulmonary valve atresia with intact ventricular septum, 1111-1112
in transposition of the great arteries, 1181
infection and, 963
side effects of, 1964, 2121
with cardiac catheterization in neonate, 1190
Prostaglandin inhibitor(s). *See also* Indomethacin
effects of
on ductus arteriosus closure, 2111
on pulmonary circulation, 374t, 377
Prosthetic valve(s)
antithrombotic therapy recommendations with, 2084t
choice of, 2212
endocarditis and, 1562
for rheumatic heart disease
recommendations for, 1521-1522, *1522*, 1523-1524
intravascular mechanical hemolysis with, *2345*, 2345
mitral, 1313, 1314
nuclear magnetic resonance and, 873
placement of. *See* Valve replacement
pregnancy with, 2382
pulmonary
in absent pulmonary valve syndrome management, 1105
St. Jude's tilting-disk, 1313, 1314
syncope due to obstruction of, 1932
thromboembolism with, 2084, 2344-2345
Protamine
adverse responses to, 2300
for heparin reversal, 2080, 2300
Protein
absorption of
in heart disease, 2358
cardiac metabolism of
regulation of, 198-199
contractile. *See* Contractile protein(s)
in renal failure management, 2436-2437
requirements for, 2354
synthesis of
genetic coding for, 5-6, 6t
Protein kinase
cAMP-dependent, 2067
Protein kinase C
alpha-adrenergic agonists in activation of, 320
Protein phosphorylation, 320
Protein-calorie malnutrition, 1669-1670, 2355t, 2355
effects on cardiac function, 2363
Protein-losing enteropathy, 2358
after intra-atrial baffle repair of transposition of the great arteries, 2260
diagnosis of, 2356
in congenital heart disease, 2355
Proteoglycan(s)
in atherosclerosis, 482
Proton(s)
nuclear magnetic resonance spectroscopy using, 615
Proto-oncogene(s), 30, 31
expression of
during cardiac myogenesis, 31-32, *33*
induction of
in cardiac hypertrophy, 41
Pro-urokinase, 2082
Pseudoaneurysm
after cardiac trauma, 2538
Pseudochylothorax, 2513
Pseudocoarctation, 1366
Pseudofusion
defined, 2153
Pseudogene(s), 17
Pseudo-Hurler polydystrophy, 1661
Pseudohypertrophic muscular dystrophy. *See* Duchenne muscular dystrophy
Pseudoinfarction(s), 1706, 1714t, 1714-1715
electrocardiographic
causes of, 746-747
Pseudomonas spp.
infective endocarditis due to, 1570
treatment of, 1572
Pseudotruncus, 1128
radiographic findings in, 703, *705*
Pseudoxanthoma elasticum, *2417*, 2417, 2430t
molecular basis of, 49
myocardial infarction in, 1713
renal anomalies in, 2430t
Psychological aspects, 2519-2527
Psychological function
impairment of
in congenital heart disease, 2311
Psychotropic drug(s)
effects on electrocardiogram, 751-752
Pteridine class agent(s), 2105
Pulmonary angioplasty. *See* Balloon angioplasty
Pulmonary artery(-ies)
anatomy of, 117
anomalies of, 1421-1452
anatomy of, 1429-1430
cardiac catheterization and angiography in, 1438-1439
classification of, 1424
course, treatment and prognosis with, 1444-1450
diagnostic evaluation of, 1431-1439, *1439*
echocardiographic examination in, 1433-1438, *1439*
embryology of, 1423, *1424*
radiologic examination in, 1431-1433
symptoms and signs of, 1431
anomalous left, *1429*, 1429-1430
course, treatment and prognosis in, 1444-1447, *1445-1446*
echocardiographic identification of, 1434-1438, *1439*
balloon dilation of. *See* Balloon angioplasty
blood flow in
Doppler assessment of, 790, *792*
velocity of, 790
velocity of, in fetus, *823*
changes in, after birth, 132, 363
conventional, 360-361
crisscross, 1129
echocardiographic assessment of, *777*, 777, *780*
elastic, 361
embryology of, 93-94, 97, 1422, *1424*
hypoplastic
echocardiographic assessment of, 777
identification of, on plain radiographs, 696
idiopathic dilation of
pulmonary valve stenosis vs., 1396
radiographic findings in, 707
in tetralogy of Fallot, 1074, *1075*
intra-acinar, 360-361
development of, 362-363
distribution of muscle in, 363
structure of, 361
muscular, 361
neomuscularization of
in pulmonary hypertension, 369, 2502
in response to hypoxia, 370
nonmuscular, 361
occult, 1430, 1447
partially muscular, 361
preacinar, 360
development of, 362, 363
structure of, 361
size of
in fetus, 819
supernumerary, 361
development of, 363
ultrastructure of, 361
unilateral absence of, 1430
course, treatment and prognosis in, 1447, *1448*

Pulmonary artery(-ies) *(cont.)*
unilateral origin of, from ascending aorta, 1430
course, treatment and prognosis in, 1447-1450, *1449-1450*
wall structure of, 361
Pulmonary artery banding
for atrioventricular canal defect, 1049
results of, 1050
for pulmonary edema in early infancy, 1967
for single ventricle, 1270, 1275
for transposition of the great arteries, 1203
for tricuspid atresia, 1123
for ventricular septal defect, 1015, 2031, *2032,* 2212-2213
Pulmonary artery branch murmur, 1922t, *1923,* 1924
Pulmonary artery catheter(s)
for monitoring during anesthesia, 2296
infections involving, 2462-2463
position of, after congenital heart disease surgery, 711
Pulmonary artery pressure, 917
changes in, at birth, 363-364
Doppler estimation of, 798
echocardiographic assessment of, 780, *781*
monitoring of, during anesthesia, 2296
postnatal fall in
altitude and, 444
pulmonary blood flow and, 365
Pulmonary artery sling, 1421, 1431, 2509
angiographic assessment of, 1445-1446, *1446*
radiographic findings in, 707
Pulmonary artery stenosis, 1409-1415. *See also* Pulmonary stenosis
abnormalities associated with, 1409
angiographic assessment of, 958t
balloon dilation for, 1413-1414, *1414,* 2198-2199, *2200*
in tetralogy of Fallot, 1088
branch
innocent pulmonary branch murmur vs., 1924
patent ductus arteriosus vs., 1066
cardiac catheterization in, 1411, *1412*
classification of, 1409
clinical features of, 1410
computed tomography assessment of, *896,* 897
differential diagnosis of, 1411-1413
echocardiographic findings in, 1410
electrocardiographic findings in, 1410, *1410*
embryology and pathology of, 1409
natural history of, 1413
pathophysiology of, 1409-1410
peripheral
intrahepatic biliary dysgenesis and, 2362
prevalence of, 1409
pulmonary valve stenosis vs., 1396
radionuclide studies in, 1410-1411, *1411*
residual, after tetralogy of Fallot repair, 1095
roentgenographic findings in, 1410, *1411*
systemic diseases associated with, 1397
treatment of, 1413-1415, *1414*
Pulmonary artery wedge angiography, 961
Pulmonary atresia
angiographic assessment of, 959t
digital subtraction angiography in, *910*
echocardiographic assessment of
in fetus, 810, *813*
nuclear magnetic resonance imaging in, 859-860, *861*
prostaglandin therapy in management of, 2119
pulmonary valve stenosis vs., 1397
tetralogy of Fallot with. *See under* Tetralogy of Fallot
with intact ventricular septum, 1108-1117
autogenous skeletal muscle enlargement of ventricle for, 1115-1116
clinical presentation of, 1110
defects associated with, 1114
differential diagnosis of, 1114
etiology of, 1108-1109
incidence of, 1108
laboratory findings in, *1111-1114,* 1111-1114
myocardial infarction in, 1686, 1712
pathology of, 1109-1110
physiology of, 1110
prognosis and future developments in, 1115-1116
surgical decisions and techniques for, 2217-2220
treatment of, 1114-1115, 1962-1963
with ventricular septal defect
angiographic assessment of, 958t-959t
echocardiographic assessment of, 777
patent ductus arteriosus vs., 1066
Pulmonary blood flow
changes in response to exercise, 431
effective, 999, 1000t
in transposition of the great arteries, 1192-1193
pulmonary artery pressure and, 365
Pulmonary branch murmur, 1922t, *1923,* 1924
Pulmonary capillary(-ies), 361
injury to endothelium of
pulmonary edema due to, 397t, *397-398,* 397-398
Pulmonary capillary wedge pressure, 917
Pulmonary circulation. *See under* Circulation
Pulmonary disease
cardiac effects of treatment of, 2506
cardiac findings in, 2501-2506
chronic
air travel and, 448
altitude and, 447-448
obstructive
airway collapse in, 352
cor pulmonale due to, 2503
restrictive
cor pulmonale due to, 2503-2504
vascular. *See* Pulmonary vascular disease
Pulmonary edema, 386-400
defined, 386
high altitude, 445, 446t
age and, 394, *395*
hydrostatic, 393-396
in congestive cardiac failure
mechanisms of, 244-245
neurogenic, 398
pathogenesis of, 393-398
pathophysiology of, 391-392
permeability, 396-398, *397-398*
causes of, 397t
safety factors protecting against, 392t, 392-393
Pulmonary embolism. *See under* Embolism
Pulmonary function test(s)
bedside
pre-extubation, 2254
Pulmonary hypertension. *See also* Pulmonary vascular disease
after atrial septal defect repair, 2028
altitude and, 444-445
consequences of, 1999-2005
drugs in treatment for, 2002t, 2002-2003
effects on cardiac function, 2502
extrinsic factors causing, 932
in atrial septal defect
physiology of, 1027
in congenital heart disease
categorization of, 2000
in cor pulmonale, 2501
in inflammatory disorders
leukocyte-induced vascular changes in, 367
in systemic lupus erythematosus, 1532
in transposition of the great arteries, 1193
persistent
after surgical ligation of patent ductus arteriosus, 2027
after ventricular septal defect repair, 2030
of newborn. *See* Persistent pulmonary hypertension of newborn
primary, 2001-2002
atrial septostomy for, 2003
pregnancy with, 2381
protocol for calculating pulmonary vascular resistance in, 933t
pulmonary vascular resistance and, 931
regression of
after surgical correction of cardiac defects, 371
reversibility of, 932, 933, 934t
structural response of pulmonary vasculature in, 369, 2502
endothelial cell's role in, 366-367, *372,* 372-373
syncope with, 1931
with high blood flow
pathophysiology of, 371-372
with right ventricular failure
difficult weaning from cardiopulmonary bypass with, 2303
with ventricular septal defect, 1006
Pulmonary infundibular stenosis. *See* Pulmonary stenosis, subvalvular
Pulmonary insufficiency
after surgery for pulmonary valve stenosis, 1405, 2035
after tetralogy of Fallot repair, 1095-1096, 2036
rheumatic aortic insufficiency vs., 1518
Pulmonary lobule
primary (acinus), *350,* 350, 360
secondary, 360
Pulmonary lymphangiectasis
severe
total anomalous pulmonary venous return vs., 697
Pulmonary murmur
innocent, *1922,* 1922t, 1923
Pulmonary nerve(s), 362
Pulmonary outflow resistance
in tetralogy of Fallot, 1078-1079
Pulmonary resistance. *See also* Pulmonary outflow resistance; Pulmonary vascular resistance
total, 931
in patent ductus arteriosus, 1059-1060, 1061
Pulmonary sequestration, 976-978, *977,* 2508
Pulmonary stenosis, 1382-1420
angiographic views for, 958t
chest pain due to, 1949
congenital
recurrence risk for, 176t
congestive heart failure due to, 2012
infundibular. *See* Pulmonary stenosis, subvalvular
murmur of
changes in, in pregnancy, 2376
Still's murmur vs., 1923
severe
tetralogy of Fallot with, 1964

subvalvular, 1406-1407
angiographic assessment of, 958t
digital subtraction angiography in, *910*
in transposition of the great arteries, 1178, 1193
in tricuspid atresia, 1119
in ventricular inversion, 1237
systemic diseases associated with, 1397
with double-outlet right ventricle, 1219, 1222
supravalvular. *See* Pulmonary artery stenosis
syncope in, 1931
valvular. *See* Pulmonary valve stenosis
ventricular inversion with, 1237
hemodynamics and physiology of, 1241
with double-outlet right ventricle, 1217-1218, 1222
corrective surgery for, 1229
Pulmonary thromboembolism. *See* Embolism, pulmonary
Pulmonary valve
absence of. *See* Absent pulmonary valve syndrome
anatomy of, *116,* 116-117
area of
calculation of, 1393
balloon dilation of, 1399-1403, *1401-1404,* 2035, 2188-2190, *2190-2192*
bicuspid, 117, 1383, *1385*
blood flow through
Doppler assessment of, 789, *790*
Doppler quantitation of, 795
velocity of, in fetus, 821
dysplastic, 1384, *1385,* 2190
angiocardiographic appearance of, 1395
echocardiographic assessment of, 774
hypoplastic, with hypoplastic annulus, 1383-1384
prosthetic
in absent pulmonary valve syndrome management, 1105
quadricuspid, 117
unicommissural, 1383, *1384*
unicuspid, 117
Pulmonary valve area
calculation of
in pulmonary valve stenosis, 1393
Pulmonary valve atresia. *See* Pulmonary atresia
Pulmonary valve stenosis, 1382-1406. *See also* Pulmonary stenosis
anatomy and pathology of, 1383-1385, *1384-1385*
angiocardiography in, 958t, 1394-1395, *1395*
body surface map findings in, 519
cardiac catheterization in, 1392-1395, *1395*
classification of severity of, 1394
computed tomography assessment of, *895,* 897
differential diagnosis of, 1395-1397
domed, 1383, *1384*
dysplastic
balloon valvuloplasty for, 1400
pulmonary valvectomy for, 1404-1405
echocardiographic findings in, 1389-1391, *1391-1392*
electrocardiographic findings in, *1388-1389,* 1388-1389
embryology of, 1383
exercise hemodynamics in, 1394
in tetralogy of Fallot, 1074, *1075*
residual, after repair, 1095
in transposition of the great arteries, 1178
in tricuspid atresia, 1119
in ventricular inversion, 1237
manifestations of, 1386-1392
mild
treatment of, 1398
mild-to-moderate
clinical features of, 1386-1387
moderate
treatment of, 1398-1399
murmur of
innocent pulmonary branch murmur vs., 1924
innocent pulmonary murmur vs., 1923
supraclavicular bruit vs., 1924
natural history of, 1397-1398
nuclear magnetic resonance in, 1392
pathophysiology of, 1385-1386
poststenotic dilation of pulmonary trunk in, 1385
pregnancy with, 2379-2380
presenting at 4-12 months
management of, 1968
prevalence of, 1382-1383
pulmonary infundibular stenosis vs., 1406
recreational, occupational and insurability recommendations for, 1405-1406
roentgenographic findings in, 707, *711,* 1389, *1390*
severe
clinical features of, 1387-1388
treatment of, 1399
systemic diseases associated with, 1397
treatment of, 1398-1405
balloon valvuloplasty, 1399-1403, *1401-1404,* 2035, 2188-2190, *2190-2192*
medical, 1398-1399
surgical, 1403-1405, 2035-2036
tricuspid, 1383
with double-outlet right ventricle, 1219, 1222
Pulmonary valvectomy
for dysplastic pulmonary valve stenosis, 1404-1405
Pulmonary valvotomy
for pulmonary valve stenosis, 1403-1405
complications of, 2035
patient selection for, 2036
residua of, 2035
sequelae of, 2035
Pulmonary valvuloplasty
balloon
for pulmonary valve stenosis, 1399-1403, *1401-1404,* 2035, 2188-2190, *2190-2192*
Pulmonary vascular disease, 1996-2006. *See also* Pulmonary hypertension
after surgery for transposition of the great arteries, 2039
altitude and, 447
assessment of, 2000-2001
atrial septal defect with, 1027-1028
prognosis in, 1036
atrioventricular canal defect with, 1040
complications of repair of, 2263-2264
management of, 1049
congenital heart defects with, 371-372
cor pulmonale due to, 2504
elective surgery and anesthesia in, 2004-2005
interventional cardiac catheterization and surgical procedures in, 2003-2004
irreversible
clinical course of, 2001
left-to-right shunt with, 1001, 1006
patent ductus arteriosus with, 1063
transposition of the great arteries with, 1202
treatment of, 2002-2004
tricuspid atresia with, 1121
ventricular arrhythmias with, 1892
ventricular septal defect with
clinical manifestations of, 1008
complications of repair of, 2263-2264
medical therapy for, 1015
Pulmonary vascular endothelium
cell culture studies of
limitations of, 368-369
functions of, 365-369
metabolic, 365t, 365-366
hemostatic potential of, *367,* 367
immunologic potential of, 367-368, 368t
in pathogenesis of pulmonary hypertension, *372,* 372-373
modulation of vascular smooth muscle reactivity by, 366-367
ultrastructure of, 361
Pulmonary vascular reactivity
assessment of, 1012-1013
Pulmonary vascular resistance. *See also* Vascular resistance
arteriolar
calculation of, in truncus arteriosus, 1132
calculation of
in atrioventricular canal defect, 1046
obtaining oxygen saturation data for, 925
protocol for, 933t
changes in
in pregnancy, 2375
in response to exercise, 431
clinical application of, 933, 934t
elevated
clinical manifestations of ventricular septal defect with, 1008
extrinsic factors causing, 932
factors affecting, 1006
factors causing changes in, 932t
in fetus, 363
indexing of, to body surface area, 933
magnitude of left-to-right shunt and, 1001
normal values for, 932
postnatal fall of, *286,* 286, 363-364
disturbance of, in hypoxic cardiomyopathy, 2480
pulmonary hypertension and, 931
units used in measurement of, 932-933
Pulmonary vasculature. *See also* Pulmonary artery(-ies); Pulmonary vein(s)
development of, 362-363
response of, to hypoxia, 369-370
structural response of
in conditions producing pulmonary hypertension, 369
structure of, 360-362
Pulmonary vein(s), 362
anatomy of, 117
anomalous connection of. *See* Anomalous pulmonary venous connection(s); Total anomalous pulmonary venous connection
balloon dilation of, 1169, 1310, 2199-2201
blood flow in
Doppler assessment of, 790-791
velocity of, 791
development of, 98, 363
echocardiographic assessment of, 775, *780*
identification of, on plain radiographs, 696
normal variation in, 1146-1147
obstruction of. *See also* Pulmonary vein atresia; Pulmonary vein stenosis
after surgery for transposition of the great arteries, 2041, 2263

Pulmonary vein(s), obstruction of *(cont.)*
intrapulmonary veno-occlusive disease vs., 2510
Pulmonary vein atresia
common, 1169-1170, 1311
anatomy of, 1169-1170
clinical features of, 1170
embryology of, 1147, 1169
hemodynamics in, 1170
management of, 1170
unilateral, 1309-1311
Pulmonary vein stenosis, *1167-1168,* 1167-1169
acquired, 1310
balloon dilation for, 1169, 1310, 2199-2201
embryology of, 1147, 1167
unilateral, 1309-1311
Pulmonary veno-occlusive disease, 2510
rheumatic mitral stenosis vs., 1511
Pulmonary venous return. *See* Anomalous pulmonary venous connection(s); Total anomalous pulmonary venous connection
Pulmonary venous wedge angiography, 961-962
Pulmonary venous wedge pressure, 919
Pulmonary-to-systemic flow ratio
calculation of
from cardiac catheterization data, 1000t
from radionuclide studies, *846,* 846
Pulmonic stenosis. *See* Pulmonary stenosis
Pulmonology, 2501-2518. *See also* Lung(s)
Pulsatility index
in fetus
age-related changes in, 822-823
Pulse (blood)
assessment of, 680-681
bounding, 680
Corrigan's, 680, 1515. *See also* Pulse, water-hammer
dorsalis pedis
congenital absence of, 680
normal rate of
age and, 680t
Quincke's, 680
in pregnancy, 2376
venous
recognition of, 682
volume of, 680
water-hammer, 680
in atrioventricular canal defect, 1041
in rheumatic aortic regurgitation, 1515
Pulse (ultrasound)
defined, 526
Pulse deficit, 680
Pulse duration
in echocardiography
defined, 526
in pacing
defined, *526,* 2153
Pulse generator. *See also* Pacemaker(s)
implantable
defined, 2153
Pulse oximetry. *See under* Oximetry
Pulse repetition frequency (PRF)
defined, *526,* 526
Pulse repetition period (PRP)
defined, *526,* 526
Pulse width
in pacing
defined, 2153
Pulsed-field gel electrophoresis, 30
Pulseless disease. *See* Takayasu's arteritis
Pulse-pair pileup, 567
Pulsus alternans, 681
in congestive heart failure, 2008
Pulsus bisferiens, 681, 1515
Pulsus paradoxus, 680-681
detection of, 2008
in pericarditis, 1592, *1594*
Pump lung, 2253
Purcell, E. M., 570
Purine
defined, 63
Purine nucleotide(s)
in DNA, *4,* 4
Purkinje cell(s)
defined, 1787
of sinus node, 122
Purkinje hamartoma
incessant ventricular tachycardia due to, 1640-1641, *1641,* 1653, 1884-1885, *1885-1887*
surgical treatment of, 2179-2181, *2180,* 2181t
Purkinje system
anatomy of, 1786-1787
electrophysiologic characteristics of, 1787, *1788*
Pyrexia. *See* Fever
Pyrimethamine
in toxoplasmosis prophylaxis and management, 2471
sulfadiazine with, 2060
Pyrimidine
defined, 63
Pyrimidine nucleotide(s)
in DNA, *4,* 4
Pyrophosphate
technetium-labeled, 564, 845. *See also* Myocardial scintigraphy, infarct-avid
Pyruvate
metabolism of, 193-194
Pyruvate dehydrogenase
in pyruvate metabolism, 193-194

Q fever
infective endocarditis due to, 1570-1571
Q value, 607
Q wave(s), 719
abnormal
differential diagnosis of, 746-747
diagnostic significance of, in children, 1685, 1700-1701
in Kawasaki disease, 746, *749,* 1701, 1702t-1703t
in myocardial infarction, 745-746, *747-748,* 1700, *1702, 1704-1705, 1707*
in myocarditis, *744,* 744
Q-OT interval, *724,* 724
serum calcium and
in newborns, 748
QR pattern, 719
differential diagnosis of, 728
in right ventricular hypertrophy, *728,* 728
QRS complex, 717-720, *719-720*
amplitude of, 719-720
axis of, 717-718, *719-720*
duration of, 717
low-voltage, 720
morphology of, 718-719
Q-T interval, 722-724, *724*
measurement of, 1876-1878
during exercise, 1889
from Holter recording, 1879
prolonged. *See also* Long Q-T syndrome(s)
mitral valve prolapse and, 1979
Quantization, 570
Quantum(s), 552
Quantum detection efficiency, 638
Quantum mottle. *See* Quantum noise
Quantum noise
in computed tomography, 629, 630
in digital subtraction angiography, 637
Quincke's pulse. *See under* Pulse
Quinidine, 2127t, 2128, 2550t
adverse reactions to, 2128
cimetidine interaction with, 2367
congestive heart failure due to, 675
dosage adjustment for renal insufficiency, 2441t
effects on electrocardiogram, 750-751, *752*
for atrial flutter, 1856
for supraventricular tachycardia, 1825
for ventricular arrhythmias, 1898
long Q-T interval due to, 1890
pharmacokinetics of, 2128, 2364t
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2365
sinus node dysfunction due to, 1775
sudden death and, 1778
syncope due to, 1941
use of, in pregnancy, 2385, 2386t
ventricular arrhythmias due to
treatment of, 1897
Quinolone(s), 2060

R wave, 718-720
abnormally tall
differential diagnosis of, 729
Rabi, I. I., 570
Rad
defined, 565
Radial artery cannulation, 2295
Radiant warmer(s), 2481
Radiation
background, 564, 565
bremsstrahlung, 552, 553, *563,* 563
characteristic, 553
definitions and laws applying to, 552-553
detection of
image quality in, *568-569,* 568-569
instrumentation for, *566-567,* 566-568
dose of, 565t, 565
in plain radiography, 692
doxorubicin cardiotoxicity and, 2339
electromagnetic, *560,* 560
in space, 435
ionizing
defined, 560
leakage, 554
maternal exposure to
hematologic and oncologic problems in child after, 2330
matter's interaction with, *562-563,* 562-563
mediastinal
late cardiac effects of, 2341-2342
particulate, 560t, 560-561
physics of, 559-569
production of, 551-553
safety issues, 555-556, 565t, 565
scattered, 637
grids for reduction of, 555, 638
thoracic
constrictive pericarditis after, 675
Radioactive decay, 559-562
modes of, 561
statistics of, 561-562, 562t, *562*

accuracy of counts, *563,* 563-564, 564t
Radiofrequency field gradient(s)
spatial localization of nuclear magnetic resonance spectra with, 613
Radiofrequency pulse(s)
artifacts due to imperfections in, 608-609
characteristics of, 587
defined, 618
depth
for localization of nuclear magnetic resonance spectra, 613
hard, 587
defined, 618
rotating magnetic field creation with, 575, *576*
sequences of, for nuclear magnetic resonance. *See under* Nuclear magnetic resonance
soft, 587
defined, 618
Radiofrequency transmitter(s)
for nuclear magnetic resonance imaging systems, 606-607, *607*
Radiography. *See also* Angiocardiography; Angiography; Computed tomography
nomenclature of x-ray projections, 954, *954-955*
plain
in congenital heart disease diagnosis, 691-712
normal anatomy of heart in, 692-695, *693-695*
radiation dose in, 692
technique for, 692
views of chest in, 692-694, *693-695*
safety of, in pregnancy, 2377
Radioligand binding
interpretation of data from, 318-319
Radionuclide
defined, 624
Radionuclide angiography. *See* Blood pool imaging; Nuclear cardiology
Radiopharmaceutical(s), 564-565
short-lived, 848-849
Radius
abnormalities of
congenital heart disease with, 678t, 678
Random hexamer labeling, 21
Randomized clinical trial, 145t, 147-148
Ranitidine
dosage adjustment for renal insufficiency, 2441t
Rapid recall response, 2240
Rashkind ASD umbrella, 2206-2208
Rashkind balloon septostomy. *See* Atrial septostomy, balloon
Rashkind Ductal Occluding Device, *1068,* 1068, 2202-2203, *2204-2207*
other applications of, 2205-2206
Rashkind septostomy catheter, *1196,* 1196
Rastan-Konno operation, *2219-2220,* 2222
Rastelli operation
for transposition of the great arteries, 1207-1209, *1208*
Rayleigh-Tyndall scattering, 535-536
Raynaud's disease, 993-994
Raynaud's phenomenon, 994
Reactance
defined, 502, *503*
Readout gradient, 588
defined, 618
Receiver
in nuclear magnetic resonance
defined, 618
Receiver coil
in nuclear magnetic resonance
defined, 618
Receptor(s), 318-324. *See also* particular types of receptors
cardiovascular
types of, 328
control of, 322-323
desensitization of, 323
theory of, 318-319
Record(s)
computerized, 663
Recovery room
physical and staffing requirements for, 2251
Recurrence risk. *See also* particular disorders
empiric data on, 175
for multifactorial disorders, 175, 176t
Recurrent laryngeal nerve
injury to
during cardiac surgery, 2313
during coarctation repair, 1370
during surgical ligation of patent ductus arteriosus, 2026
Red blood cell(s)
altitude's effects on, 443-444
technetium-labeled, 564
Red-neck syndrome, 2058-2059
Reducing body myopathy, 2321
Redundant cusp syndrome. *See* Mitral valve prolapse
Reentry
in atrial flutter, 1849-1850
in supraventricular tachycardia
with bypass tracts, 1837-1842, *1839*
without bypass tracts, 1832-1837
mechanisms of arrhythmias due to, 311-312, *312*
Reference program(s)
computer-based, 644
Reflection
mechanisms of arrhythmias due to, 313, *314*
Reflection coefficient
pulmonary fluid balance and, 391
Reflex apnea, 1431
Refractoriness, *298,* 298
age-related changes in, 309
in disease, 310
Refractory period, *298,* 298
of pacemaker, 2144, 2154
Refsum disease, 1668
Regitine. *See* Phentolamine
Regression analysis, 654
repeated-measures, 652
Regulation
defined, 546
Regulative development, 158
Regulatory gene
defined, 63
Regulatory sequence
defined, 63
Regurgitant fraction(s)
from Doppler echocardiography, 796
from equilibrium blood pool imaging, 840
from first-pass blood pool imaging, 841
Regurgitant lesion(s). *See also* particular lesions
anatomic location of
clinical significance of, 1305
assessment of severity of, 1306
clinical physiology of, 1304t, 1304-1307
Rehabilitation. *See* Cardiac rehabilitation
Reid's syndrome. *See* Mitral valve prolapse
Reiter's syndrome, 1536, 1537
Rejection, 2236
acute
immunologic basis for, 2242
treatment of, 2498
future directions in management of, 2247-2249, *2248-2249*
hyperacute
immunologic basis for, 2242
immunologic basis for, 2241-2242, *2242*
predictive tests of, 2242
staging of, 2242
Relative(s)
first-degree
defined, 171
second-degree
defined, 171
third-degree
defined, 171
Relaxation
quadrapolar, 616
Relaxation time(s)
in nuclear magnetic resonance. *See under* Nuclear magnetic resonance
Relaxing factor, 203
Reliability
in epidemiologic studies, 148
Rem
defined, 565
Renal angiography, 984-988
Renal artery disease
systemic hypertension due to, 1993
Renal blood flow
autoregulation of, 451
calculation of, 451
developmental aspects of, 464
distribution of, 451
dynamics of, 450-451
Renal failure
acute
after cardiac surgery, 2433-2439
cardiac manifestations of, 2428-2431
causes of, 2431t
complications of, 2435, 2435t
congestive heart failure due to, 2012-2013
defined, 2428
intrinsic, 2428
postrenal, 2428
prerenal, 2428
prerenal azotemia vs., 2435t, 2435
prevention of, 2435-2436
principles of management of, in recovery room, 2436
antibiotic dose adjustment in, 2049t
chronic
cardiac manifestations of, 2431-2433
echocardiographic assessment in, 2431-2432, 2432t
hemoglobinuric, 2437
postoperative, 2261-2262, 2433-2439
causes of, 2433-2434
diagnosis of, 2434-2435, 2435t
management of, 2436-2439
Renal function, 450-467, *2100*
age-related differences in, 2099
developmental aspects of, 464-465
glomerular, 451-453, *452,* 452t
in neonate, 471
in coarctation of the aorta, 2427
in congestive heart failure, 2425-2427
indomethacin's effects on, 2117-2118
metabolic and endocrine, 462t, 462-464
normal cardiac relationship to, 2425
tubular, *453,* 453-454
developmental aspects of, 465
in neonate, 471

Renal insufficiency
modifications of drug therapy in, 2439, 2440t-2441t
Rendell-Baker-Soucek mask, 2291
Renin. *See also* Renin-angiotensin-aldosterone system
mechanisms for release of, 463-464
Renin-angiotensin-aldosterone system, 458, *463*, 463-464
in congestive heart failure, 340
Reperfusion
injury due to, 267-270, 1691
myocellular effects of, 267-270
surgical
in myocardial infarction management, 1718-1719
Repetition time (TR)
defined, 618
Requirement
defined, 546
Research
applied, 643
basic, 643
collaboration in, 643, 645
defined, 642
descriptive, 643
design of, 642-645
elements of, 643t, 643-645
sample size calculation in, 653-654
experimental, 642-643
types of, 642-643
Reserpine
effects on pulmonary circulation, 374t, 376
Residual volume, 353
Resistance
airway, 352-353
electrical
defined, 502, *503*, 2140
pulmonary. *See* Pulmonary resistance
vascular. *See* Vascular resistance
Resistance ratio, 931-932
normal, 932
Resolution
axial
defined, 768
azimuthal
defined, 768
defined, 628
lateral
defined, 768
measurement of
in x-ray imaging system, 629
Resonance, 572, *573*
defined, 618
Resonant frequency
defined, 618
Respiration. *See also* Ventilation
control of, 197, 357-358
during exercise, 431-432
electrocardiographic artifact due to, 754, *758*, 764
heart rate response to
in parasympathetic neuronal function evaluation, 335
open heart surgery's effects on, 2253
postoperative assessment of, 2251-2252
upper limit of rate of
age and, 674t
Respiratory acidosis. *See also* Acidosis
in development of cor pulmonale, 2502
postoperative, 2253
Respiratory care
for neonate, 2482-2483
Respiratory center abnormality(-ies)
cor pulmonale due to, 2504
Respiratory exchange ratio. *See* Respiratory quotient
Respiratory gas exchange, 349-350
measurement of
equipment for, 2269
in exercise testing, *831*, 831-832, 833
Respiratory muscle(s), 354-355
Respiratory quotient, 429, 928
Respiratory spectrometer
for automated exercise testing, *831*, 831
Resting membrane potential, 294-295, *295*
of embryonic heart, 308
of neonatal heart, 309
Restriction enzyme(s), 7, *7-8*, 63
discovery of, 6-7
in DNA analysis, 20-21
properties of, 22t
Restriction enzyme mapping, 28, 63
Restriction fragment length polymorphism (RFLP), 21-23, *24-25*
defined, 63
Restrictive cardiomyopathy. *See* Cardiomyopathy(-ies), nondilated
Restrictive lung disease
cor pulmonale due to, 2503-2504
Resuscitation. *See* Cardiopulmonary resuscitation
Retinal artery(-ies)
in coarctation of the aorta, *1359*, 1359
Retinoic acid
heart defects associated with neural crest injury and, 162
Retinopathy
in congenital heart disease, 2311
Reverse genetics, 27
Reverse transcriptase, 7
defined, 63
Reversion
in pacing
defined, 2154
Rewarming acidosis, 2302
Reye's syndrome
risk of
influenza vaccination and, 2473
Reynolds number, 536, 598, 1919
Rhabdomyoma, *1649*, 1650-1651, *1651-1653*
therapy for, 1654
Rheumatic arthritis, 1491, 1492
Rheumatic endocarditis, *1491*, 1491
Rheumatic fever, 1485-1501. *See also* Rheumatic heart disease
changes in severity, presentation and course of, 1495, *1496-1497*
chronic
in pregnancy, 2377-2378
clinical manifestations of, 1492-1495
conduction abnormalities in, 1491
congestive heart failure due to, 2015
course and prognosis in, 1498
criteria for diagnosis of, 1492t, 1492-1495
defined, 1485
differential diagnosis of, 1495-1498
epidemiology of, 1487-1488
genetic predisposition to, 1488
in pregnancy, 2377
Lyme disease vs., 1538
pathogenesis of, 1488-1490, *1489*
pathology of, *1490-1491*, 1490-1491
recurrence of, 1498
streptococcus and, 1485-1486
treatment of, 1498-1500
prophylactic, 1498-1499, 2050
Rheumatic heart disease, 1502-1526. *See also* particular lesions
arrhythmias in, 1520
physical activity in, 1520
treatment of, 1520-1524, *1521-1522*, 1523t
prophylactic, 1520, 2050
surgical, 1521-1524, 1523t
Rheumatic myocarditis, 1490-1491, 1493
Rheumatic pancarditis, 1490-1491
Rheumatic pericarditis, 1490, *1491*, 1493
Rheumatoid arthritis
juvenile, 1527-1529
cardiovascular manifestations of, 1528-1529
classification of, 1527-1528
congestive heart failure due to, 2015
criteria for diagnosis of, 1527
Kawasaki disease vs., 1549
Lyme disease vs., 1538
rheumatic fever vs., 1497
Ribavirin, 2061
Rib-notching
in coarctation of the aorta, 1360
Ribonucleic acid (RNA)
alternative splicing of, 18-20, *19*
composition of, 14
cytoplasmic
classes of, 5
discovery of, 3
heterogeneous nuclear (hnRNA), 18
defined, 62
messenger (mRNA), 5
coding region of, defined, 61
complex formation, with ribosome, 20
defined, 62
storage of, 20
translation of, 20
turnover of, 20
nucleocytoplasmic transport of, 18
processing of, 18
ribosomal (rRNA), 5
splicing of, 9-10, *12*
defined, 63
structure of, 5
synthesis of, 14
transfer (tRNA), 5
Rickettsial disease(s)
cardiac manifestations of, 2471
Rifampin, 2060
anticoagulant interaction with, 2052
for tuberculosis, 2060
vancomycin synergism with, 2058
Right atrial isomerism. *See* Asplenia syndrome
Right atrial pressure, 918
Right atrium
anatomy of, 112-114, *113*
blood flow in
Doppler assessment of, 788
enlargement of
electrocardiographic findings in, 731-732, *732*
in fetus
echocardiographic assessment of, 807, *808*
in pulmonary valve atresia with intact ventricular septum, 1110
morphologic characteristics of, 1233, 1282
Right bundle branch, *124*, 124-125
anatomy of, *1786*, 1786-1787
electrophysiologic characteristics of, 1787, *1788*
Right bundle branch block, 1787-1789, *1788-1790*
after tetralogy of Fallot repair, 2036-2037

after ventriculotomy, 2030
central vs. peripheral, 1788-1789, *1789*
complete
causes of, 734
electrocardiographic findings in, 733-734, *734*
electrocardiographic findings in, 733-735, *734*
incomplete, 1789, *1791*
atrial septal defect and, 1030
cause of, 734
electrocardiographic findings in, *734,* 734-735
left anterior hemiblock with, 737, *738*
myocardial infarction diagnosis in presence of, 1706t, 1706, *1707*
postoperative, 2258
Right isomerism. *See* Asplenia syndrome
Right subclavian artery
anomalous, *1427,* 1427-1428, 2509
computed tomography assessment of, *890*
course, treatment and prognosis in, 1439-1440, *1440*
embryology of, 1423
signs and symptoms of, 1431
formation of, 93, 96
Right ventricle
anatomy of, 114-116
double-chambered, 1407-1409, *1408-1409*
double-outlet. *See* Double-outlet right ventricle
dysfunction of
after tetralogy of Fallot repair, 1096
fetal
echocardiographic assessment of, *808,* 808-810, *810-811*
in congestive heart failure, 248
in Ebstein's anomaly, 1135
in pulmonary valve atresia with intact ventricular septum, 1109
in tricuspid atresia, *1119,* 1119
intracavitary obstruction of, 1406-1409
morphologic changes in, after birth, 132
morphologic characteristics of, 1233, 1282
on echocardiography, 772, 1242
parchment, 1893
suicide
after pulmonary valvotomy, 1404
systemic function of
after atrial baffle procedure, 1206
Right ventricular dysplasia
arrhythmogenic. *See* Arrhythmogenic right ventricular dysplasia
Right ventricular hypertrophy. *See under* Ventricular hypertrophy
Right ventricular inflow
Doppler assessment of, 788-789, *789*
Right ventricular outflow
Doppler assessment of, 789, *790-791*
obstruction of. *See also* Pulmonary stenosis
management of, in first two weeks of life, 1964
physiology of atrial septal defect with, 1027
repair of, in tetralogy of Fallot, *1093,* 1093-1094
ventricular septal defect with, 1005
Right ventricular outflow tract
in atrioventricular canal defect
echocardiographic examination of, 1044
in tetralogy of Fallot, 1073-1074
terminology of, 115-116
Right ventricular pressure
diastolic
measurement of, 918
systolic
Doppler estimation of, 797-798, *798*
electrocardiographic calculation of, 729
measurement of, 917-918
Right ventricular strain pattern, 729
Right-axis deviation, 717
in right ventricular hypertrophy, 730
Right-hand rule
for magnetic field direction, 586
for ventricular architecture, *1249,* 1249
Right-to-left shunt(s)
after Mustard operation for transposition of the great arteries, 2039
brain abscess and, 2308
clinical physiology of, 1070-1072
complications and sequelae of, 1072
detection of
by indicator dilution, 937, *937*
by oximetry, 919t
by radionuclide tracer flow analysis, 846
by vascular perfusion imaging, 847
determinants of degree of, 1070-1072
inhalation anesthesia with, 2294
intravenous anesthesia with, 2295
obstetric anesthesia with, 2390
physiological, 925
quantitation of, 1070, 1071t
by indicator dilution, 938-939, *939*
by oximetry, 921t, *922,* 922
thermodilution measurements in presence of, 940
with atrial septal defect, 1026, 1027
with patent ductus arteriosus, 1060, 1061
Right-to-left ventricular pressure ratio
postoperative
prediction of, in tetralogy of Fallot management, 1093
Riley-Day syndrome, 339-340
Ringer, Sidney, 202, 643
Ringing artifact, 609
Risk
defined, 141
relative
defined, 146
Risk factor(s)
for cardiovascular disease, 475, 488-489, 1713t, 1989-1993
RNA. *See* Ribonucleic acid
RNA polymerase
binding of, 16
Ro antibody
in neonatal lupus erythematosus, 1534, 1535
Rocephin. *See* Ceftriaxone
"Rocker-bottom" feet
in trisomy 18, *182,* 182
Rocky Mountain spotted fever, 2471
Roentgen
defined, 565
Roentgen, Wilhelm Konrad, 552
Roentgen ray(s). *See* X-ray(s)
Roentgenography. *See* Radiography
Roger's disease, 1002
Romano-Ward syndrome, 341, 752, 1889. *See also* Long Q-T syndrome(s)
molecular basis of, 55
syncope in, 1932
R-on-T phenomenon, 1871
in children with otherwise normal heart, 1887
Rotating frame of reference, 575-576, *577*
defined, 618
Rotating frame zeumatography, 613
Roth spot(s)
in infective endocarditis, 1564
Rough zone, 114
RSR′ pattern, 718-719
in right ventricular hypertrophy, 729-730, *730*
Rubella
congenital, 676t, 676, 980-981, 2472
cardiac and renal anomalies due to, 2430t
cutaneous manifestations of, 2421
endocrine abnormalities due to, 2498t, 2499
myocarditis due to, 1579
oncocytic cardiomyopathy and, 1641
patent ductus arteriosus due to, 1056
pulmonary artery stenosis due to, 1409, 1410
Rubidium-82
blood flow measurement using, 495
positron emission tomography using, 620, 875
Rubinstein-Taybi syndrome, 2411
cardiac and renal anomalies in, 2429t
congenital heart disease in, 678t, 679
orthopedic problems in, 2457-2458
Rule
defined, 546
Rupture
aortic
coarctation of the aorta and, 1367
cardiac, 2536-2537
Ryanodine
effect on delayed afterdepolarizations, 315
inhibition of calcium release by, 206

S wave, 718-720
deep
differential diagnosis of, 729
S1 nuclease mapping, 27
defined, 63
Sacrocardinal vein(s), 100
Saint Vitus' dance. *See* Sydenham's chorea
Salicylism
tachypnea due to
heart failure vs., in rheumatic fever, 1493
Salmonella aortitis, 2469
Salmonella arteritis, 2469
Salmonella typhi infection, 2469
Sandhoff disease, 1663
Sanfilippo syndrome, 1660, 2406t, 2406
Sanger-Coulsen method
for DNA sequencing, 23
Saphenous nerve
injury to
due to cardiac surgery, 2313
Saralasin
effects on pulmonary circulation, 374t, 378
Sarcoidosis, 2420-2421, *2421*
electrocardiographic findings in, 754
Sarcolemma
calcium movements across
control of, 204-205, 205t
during development, 208-209, *210*
electron microscopic features of, 128-130, *130*
morphologic changes in, during cardiac maturation, 208
Sarcomere
electron microscopic features of, 130, *131*
organization of, *212,* 212
Sarcoplasmic reticulum
calcium movements across
control of, 205-207
during development, 209, *210*
corbular, 205
electron microscopic features of, 130
form of, 205

Sarcoplasmic reticulum *(cont.)*
morphologic changes in, during cardiac maturation, 208, *209*
protein composition of, 206t, 206
Satellite cell(s), 165
Saturation
in nuclear magnetic resonance, 594
Saturation transfer
nuclear magnetic resonance evaluation of reaction kinetics by, 611-612
Scalene muscle(s)
in ventilation, 354
Scarlet fever
Kawasaki disease vs., 1549
rheumatic fever and, 1495
Scatter. *See under* Radiation
Scavenger receptor, 482
Scheie's syndrome, 1659, 2406t, 2406, 2418
Schinzel-Giedion syndrome, 2430t
Schlicter test, 1571
Sciatic artery
persistence of, 988
Scimitar syndrome, *1148,* 1148, 2507-2508
cardiac catheterization and angiographic findings in, 1152
clinical features of, 1150, 2507
dextrocardia and, 1283-1284, 1285, *1285*
radiographic features of, 1150, *1151,* 2507-2508
atrial septal defect vs., 697, *698*
surgical treatment of, 1152, 2508
Scintigraphy. *See* Nuclear cardiology; particular techniques
Scintillation
defined, 624
Scintillation camera(s). *See* Gamma camera(s)
Scleroderma
electrocardiographic findings in, 754
Scoliosis, 2445-2451
cardiopulmonary function in, 2447-2449
congenital, *2446,* 2446
electrocardiographic abnormalities in, 2449t, 2449
idiopathic, 2445-2446
etiology of, 2445
patterns of curves in, 2445-2446
idiopathic-like, 2446
in congenital heart disease, 678, 2449-2451
etiology of, 2450-2451
identification of, 2451
management of, 2451, *2451-2452*
in Marfan syndrome, 2460
in Noonan syndrome, 2457
in paraplegia due to ischemic spinal cord injury, 2456
in spastic hemiplegia, 2455
in tricuspid atresia, 1121
in Turner syndrome, 2456
measurement of curve in, 2446-2447, *2449*
nonstructural, 2445
orthopedic aspects of, 2445-2449
physical evaluation of, 2446, *2447-2448*
radiographic assessment in, 2446
structural, 2445
Scopolamine
premedication with, 2291
Scorpion sting, 1671
Second gas effect, 2294
Sedative(s), 2553t
Sedative-hypnotic agent(s)
for obstetric analgesia, 2389
Seizure(s), 2321-2322
atonic, 1940
breathholding spells vs., 2323
electrocardiographic artifact due to, 754, *757*
hyperadrenergic dysautonomia due to, 338
in long Q-T syndrome, 2322-2323
postoperative, 2258-2259
syncope due to, 1940
syncope vs., 1941, 2322
syncope with, 1726
Selenium, 1666, 2363
Semilunar valve(s). *See also* Aortic valve; Pulmonary valve
echocardiographic assessment of, 774
in fetus, 810-811
formation of, 89-90, *93*
light microscopic features of, 128
Senning operation, 1203-1204, *1204,* 2213, *2214. See also* Atrial baffle procedure(s)
angiographic views for assessment of, 959t
arrhythmias after, 1776, 2263
electrophysiology of, 2159
balloon dilation for venous baffle obstruction after, 2197-2198
complications of, 1205-1206, 2263
Sensing threshold
in pacing
defined, 2154
Sensitive-point method
spatial localization of nuclear magnetic resonance spectra by, 613
Sensitivity
in pacing
defined, 2154
of diagnostic tests, 142-144, *143-144*
Sepsis
myocarditis vs., 1585
pulmonary capillary endothelium injury due to, 397-398, *398*
Septal band, 115-116, *116*
Septal defect(s). *See also* Atrial septal defect; Ventricular septal defect
familial
molecular basis of, 55
Septation, 82-89, *84*
for single ventricle, 1273-1274, *1274*
Septic shock
cardiac manifestations of, 2470-2471
Septostomy. *See* Atrial septostomy
Septra. *See* Trimethoprim-sulfamethoxazole
Septum primum, 85, 1024
displacement of
in hypoplastic left heart syndrome, *1317,* 1317, 1318
Septum secundum, 1025
Septum spurium, 84
Sequestration
pulmonary, 976-978, *977,* 2508
Serotonin
effects on pulmonary circulation, 374t, 376
metabolism of
in lungs, 366
Serratus muscle(s)
in ventilation, 354
Serum sickness
rheumatic fever vs., 1497
Sex
congenital heart disease and, 677
Sex hormone(s)
maternal use of
congenital heart disease and, 676
Sexuality
counseling patient on, 2371-2372
parental attitudes toward, 2524
SGOT. *See* Glutamic-oxaloacetic transaminase, serum
Shadowing, 531
Shear stress
cardiac morphogenesis and, 167
vasodilation in response to, 484
Shift reagent(s), 616
Shimming, 606
Shine-Dalgarno sequence
defined, 63
Shock
cardiogenic
with myocardial infarction, 1716, 2283
gram-negative endotoxin
cardiac manifestations of, 2470-2471
in critically ill neonates
vasodilators in management of, 2095-2096
Shock liver, 2360-2361
Shone's syndrome, 1306, 1356
Shortening fraction, *227,* 227
Shprintzen syndrome, 2402-2403
Shunt(s)
bidirectional
quantitation of, 922-923, *923-924,* 940
computed tomography assessment of, 903
for hydrocephalus
infections involving, 2463
left-to-right. *See* Left-to-right shunt(s)
"net"
validity of, 923
oximetric detection of, 919t, 919-921
oximetric quantitation of, 921t, 921-926, *922-924*
oximetry in presence of, 920-921
palliative. *See also* particular procedures
choice of, 2211-2212
for single ventricle, 1268-1270
for tetralogy of Fallot, sequelae of takedown of, 2037-2038
nuclear magnetic resonance imaging of, 860, *861-862*
postoperative complications of, 2264
vascular perfusion imaging of, 847, *848*
pleuroperitoneal, 2514
right-to-left. *See* Right-to-left shunt(s)
Shy-Drager syndrome, 338-339
Sialidosis, 1661-1662
Sibling(s)
reactions to congenital heart disease, 2522-2523
Sick euthyroid syndrome, 2493
Sick sinus syndrome. *See also* Sinus node dysfunction
after atrial septal defect repair, 2029
after Mustard operation, 1205
bradycardia with
ventricular arrhythmias with, 1891
problems with term, 1751
sudden death and, 1912-1913
syncope in, 1934, *1937*
Sickle cell disease, 1670-1671, 2334-2335
altitude and, 448
rheumatic fever vs., 1497
Signal averaging technique
in electrocardiography, 520-521, *521*
Signal-to-noise ratio
in nuclear magnetic resonance imaging, 866-867
Significance
statistical, 149, 648
Simulation method(s)
educational software using, 665-666
Single photon emission computerized tomography (SPECT)

myocardial imaging with, 844
Single ventricle, 1246-1279
anatomy of, 1249-1255, *1250*
angiography in, 960t, 1265, *1266-1269*
cardiac catheterization in, 1264-1265
classification of, *1247*, 1247
clinical findings in, 1259-1261
conduction system in, 1253-1255, *1254*, 1256t, *1256*, 1787
coronary arteries in, 1252-1253
diagnosis of, 1261-1263
prenatal, 1275
echocardiographic findings in, 770, *770-771*, 771, 1263-1264
electrocardiographic findings in, 1263
embryology of, 1255-1257, *1258*
incidence of, 1257-1259, 1258t-1263t
management of, 1266-1275, 1967
"curative" procedures for, 1271-1274, *1272-1274*
palliative procedures for, 1266-1271
modes of atrioventricular connection in, 1247-1248, *1248*
natural history of, 1266
nomenclature of, 1247-1249, *1248-1249*, 1250t
nuclear magnetic resonance imaging in, 1264
radioisotope studies in, 1264
roentgenographic findings in, 1263
synonyms for, 1246t
ventricular function assessment in, 1264
with dominant left ventricle, 1240, 1249, 1250-1251, *1252*
conduction system in, 1253-1255, *1254*, *1256*
coronary artery anomalies in, 1250, 1459-1460, *1460*
embryology of, 1256-1257
with dominant right ventricle, 1249-1250, 1251-1252
conduction system in, 1255
embryology of, 1257
with indeterminate ventricular morphology, 1250, 1252
conduction system in, 1255
Single-blind study design, 147
Sinoatrial exit block, 1757-1759, *1760*
Sinoatrial groove, 80
Sinoatrial node. *See* Sinus node
Sinoatrial ring, *103*, 104
Sinotubular ridge, *120*, 120
Sinoventricular conduction
in hyperkalemia, 747
Sinus arrest. *See* Sinus pause
Sinus arrhythmia, *1754*, 1952, *1953*
defined, 1755-1756
extreme, 1952
physiologic, 680
quantitation of
in syncope diagnosis, 1945
respiratory, 1952
in parasympathetic neuronal function evaluation, 335
sinoatrial exit block vs., 1758
symptomatic, 1953-1954
Sinus bradycardia, 1753-1755, *1754*, 1755t, 1952
differential diagnosis of, 1755, *1755-1756*
persistent
fetal, 1907
symptomatic, 1953-1954
with myocardial infarction, 1715
management of, 1718
Sinus node, 121-123, *123*
cellular electrophysiology of, 1751
development of, 104
evaluation of function of
indications for electrophysiology studies, 1773
on electrophysiology studies, 1744-1746, *1746-1747*
on exercise electrocardiography, 1737-1738
intraoperative injury to, 2257-2258
location of, 113, 1776-1777, *1777*
Sinus node artery, 121, 125, 1453, 1454
in transposition of the great arteries, 1177
location of, 1776-1777, *1777*
Sinus node dysfunction, 1751-1785, 2322. *See also* Sick sinus syndrome
causes of, 1774t-1775t, 1774-1776
clinical associations with, 1773-1776
criteria for
electrocardiographic, 1753t, 1753-1760
electrophysiologic, 1772t, 1772-1773
diagnosis of, 1751-1772
atrial recording and pacing with temporary epicardial electrodes in, 1762-1763, *1764-1766*
electrocardiographic, 1751-1760, *1752-1763*, 1753t
exercise testing in, 1760-1762, *1764*
intracardiac electrophysiology in, 1763-1773, *1766-1771*, 1772t
pharmacologic autonomic manipulation in, 1772
transesophageal atrial recording and pacing in, 1762, *1763*
pacemaker implantation for, *1779*, 1780
indications for, 1778-1779, 2137-2138, *2138*
prevention of, 1776-1777, *1777*
sudden death and, 1912-1913
symptoms of, 1773-1774
treatment of, 1776-1780
indications for, 1777-1779
Sinus node recovery time, 1744
measurement of, 1765-1768, *1767-1768*
Sinus(es) of Valsalva, 116, 120, 1453
ruptured, with fistula
patent ductus arteriosus vs., 1065
Sinus pause, 1756, *1757-1758*
fetal, 1907
in normal subjects, 1952
Sinus tachycardia, 680
atrial ectopic focus tachycardia vs., 1844
characteristics of, 2546t
clinical situations associated with, 1819
pathologic tachycardia vs.
pacemaker differentiation of, *2158-2159*, 2159
reentry
in sinus node dysfunction diagnosis, 1772
supraventricular tachycardia vs., 1818-1820, *1819*
with myocardial infarction, 1715
management of, 1718
Sinus venosus
changes in, *84*, 84-85
Sinusitis, 2467
Sisomicin, 2056
Situs, 109. *See also* Situs inversus; Situs solitus
echocardiographic assessment of, 769, *770*, *778*
in fetus, 807, *808*
electrocardiographic assessment of, 724, *725*
indeterminate. *See also* Asplenia syndrome; Polysplenia syndrome
defined, 1280
radiographic assessment of, 694-695, *1468*, 1468
systemic venous return anomalies and, 1462, *1463*
Situs ambiguous. *See also* Asplenia syndrome; Polysplenia syndrome
defined, 1280
Situs inversus, 109
defined, 1281
dextrocardia with
cardiac abnormalities associated with, 1284t, 1284-1285, *1286*
echocardiographic findings in, 769
in fetus, 807
electrocardiographic findings in, 724, *725*
incidence, genetics and etiology of, 1282
levocardia with, 1285, *1287-1288*
radiographic findings in, 694-695
ventricular inversion and normally connected great arteries with, 1236
Situs solitus, 109
defined, 1281
echocardiographic findings in, 769
in fetus, 807, *808*
radiographic findings in, 694
Skeletal abnormalities. *See also* Orthopedics
congenital heart disease with, 678
Skin
diseases of
cardiovascular disease confused with, 2423
cardiovascular disease with, 2422
in electrocardiography, 502-503
involvement of, in cardiac disease, 2414-2424
due to drug therapy, 2422
due to genetic diseases, 2414-2418
due to infectious diseases, 2421-2422
due to systemic diseases, 2418-2421
Skin fat-fold measurement, 2356
Skin fibroblast culture(s)
for chromosome analysis, 178
Sleep
respiratory mechanics during, 354
Slew rate
defined, 2154
Slice thickness
defined, 618
Sliding filament theory. *See* Cross-bridge(s)
Slipped capital femoral epiphysis
in Down syndrome, 2456
Slipping rib syndrome, 1948
Slow atrial pacing method
for sinoatrial conduction time assessment, 1770-1771, *1771*
"Sluice flow" phenomenon, 281
Sly syndrome, 1661, 2406t
Small airway disease
airway resistance in, 352
Small cardiac vein, 126
Smith-Lemli-Opitz syndrome, 2404, *2405*
Smoking
by congenital heart disease patients, 2525-2526
coronary artery disease and, 1990, 2281
Smooth muscle cell(s)
arterial, 484-485
endothelial cells' effects on, 366-367, 486
in atherosclerosis, *484*, 484-485
in pulmonary arteries, 361
alterations in, in pulmonary hypertension, 370
lipid ingestion by, 482

Snowman sign
in total anomalous pulmonary venous connection, 697, *1159,* 1159
Social Security Disability Insurance (SSDI), 2529-2530
Sodium. *See also* Hypernatremia; Hyponatremia; Sodium balance
fractional excretion of
in acute renal failure diagnosis, 2436
in extended-spectrum penicillins, 2053
in tubular hydrogen ion secretion, 460-461
intracellular
nuclear magnetic resonance studies of, 616
renal transport of
regulation of, *2100*
resting membrane potential and, 295
retention of
in compensation of congestive cardiac failure, 244-245
tubular transport of, 453-454
Sodium balance
renal regulation of, 456-459, *457,* 458t
sensing receptors in, 457, 457t
Sodium bicarbonate, 2553t
in cardiopulmonary resuscitation, 413-417
detrimental effects of, 414-415, *415,* 417
in neonatal resuscitation, 2478
Sodium channel
agents affecting, 2069
characteristics of, 302-304, *303-304*
Hodgkin-Huxley model of, 302, *303*
Sodium chloride
tubular transport of, 453-454
Sodium nitroprusside. *See* Nitroprusside
Sodium window current, 304
Sodium-23
nuclear magnetic resonance spectroscopy using, 615-616
Sodium-calcium exchanger
of mitochondria, 207
of sarcolemma, 204-205, 205t, 2066, *2067*
during development, 208
in action potential, 307-308
resting membrane potential and, 295
Sodium-potassium pump
resting membrane potential and, 295
Software, 660-666
charting, 664, *665*
communications, 664
database, 662-663, *663*
defined, 657
educational, 665-666
for digital subtraction angiography system, 639
graphics, 664, *665*
spreadsheet, 663-664
statistics, 647, 664-665
word processing, 662
Soldier's patches, 110
Somatotropin. *See* Growth hormone
Somite(s)
number of
age correlation with, 71, 72t
Sotalol, 2551t
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2365
Southern blotting, *9,* 9
defined, 63
in DNA analysis, 21, *23*
Space
birth, growth and development in, *438,* 438-439, 439t
cardiovascular developmental physiology in, 435-440
environment of, 435, *436*
Spatial distortion
in digital subtraction angiography, 638
Spatial pulse length (SPL)
defined, *526,* 526
Spatial resolution
defined, 568
of gamma cameras
measurement of, *568-569,* 568-569
x-ray system evaluation using, 629
Specification
defined, 546
Specificity
of diagnostic tests, 142-144, *143-144*
Spectrometer
nuclear magnetic resonance
defined, 618
respiratory
for automated exercise testing, *831,* 831
Spectrophotometric method
oxygen saturation determination by, 920
Spectroscopy
nuclear magnetic resonance. *See under* Nuclear magnetic resonance
Sphingomyelinase deficiency
in Niemann-Pick disease, 1662
Spillover effect
in positron emission tomography studies, 620
Spin
defined, 616
Spin density
defined, 618
Spin echo. *See also under* Nuclear magnetic resonance
defined, 583, 618
Spinal cord injury
ischemic
complicating coarctation repair, 1371, 2259
in surgery for congenital heart disease, 2313, 2455-2456
with coarctation of the aorta, 2311
Spinal muscular atrophy
type IV, 2459
Spin-spin coupling, 611
Spiral-stream theory, 166
Spironolactone (Aldactone), 2102t, 2105-2106, 2548t
dosage adjustment for renal insufficiency, 2441t
in congenital heart disease management in neonates, 1966
in congestive heart failure management, 2016
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2366
use of, during pregnancy, 2387t
Spleen
clinical assessment of, 683
therapeutic infarction of, 984
Splenic flexure syndrome, 1949
Splenic sequestration syndrome
pain in, 1948
Splenoportography, 981, *984*
Spliceosome, 19
Splicing, 9-10, *12*
Splinter hemorrhage(s)
in infective endocarditis, 2422
Split gene
defined, 63
Spondyloarthropathy(-ies), 1536-1537
Sports. *See* Athletics
Spreadsheet(s)
electronic, 663-664
Squatting, 673
in tetralogy of Fallot patients, 1079
ST segment, 720
elevated
differential diagnosis of, 744-745
Stadol
for obstetric analgesia, 2387t
Staging
of rejection, 2242
Stahl, Franklin, 5
Standard(s), 545-547
Standard deviation, 649
Standard error of the mean, 649
Standing
hemodynamic and plasma catecholamine response to
in sympathetic neuronal function evaluation, 333
Staphylococcus aureus
cardiovascular manifestations of infection with, 2469-2470, *2470*
endocarditis due to, 1569-1570
treatment of, 1572
methicillin-resistant
cephalosporin susceptibility of, 2053
pericarditis due to, 1591
treatment of, 1597
Staphylococcus epidermidis
endocarditis due to, 1570
treatment of, 1572
Staphylococcus spp. *See also* Staphylococcus aureus; Staphylococcus epidermidis
endocarditis due to, 1569-1570
Starch(es)
low molecular weight
in nutritional therapy, 2357
Starling, E. H., 232
Starling forces
in tubular reabsorption of sodium, 458
Statistician(s)
when to consult, 646-647
Statistics, 646-655
computer programs for, 664-665
intuitive, 649-650, *650*
types of errors in, 651
Steady-state free precession, 613
Steell, Graham, 688t
Steinberg sign, 2398
Steinert disease. *See* Myotonic dystrophy
Stellate ganglionectomy
for long Q-T syndrome, 1890
for ventricular arrhythmias, 1900
Stent(s)
intravascular. *See* Vascular stent(s)
Steric blocking, 215
Sterilization
permanent, 2373
Stern, O., 570
Sternocleidomastoid muscle(s)
in ventilation, 354
Sternotomy
wound infection after, 2463-2464, *2464*
Steroid(s)
alternate-day therapy with, 2496-2497, 2497t
antenatal
effects on patent ductus arteriosus, 2118
anti-inflammatory therapy with, 2496-2497, 2497t
for brain abscess, 2467
for connective tissue diseases, 2497

for immunosuppression after heart transplantation, 2235, 2244, 2497-2498
for Kawasaki disease, 1556
for myocarditis, 2497
for postpericardiotomy syndrome, 1602
for rheumatic fever, 1499
for septic shock, 2470
for systemic lupus erythematosus, 1531
coronary artery disease and, 1531-1532
for vascular malformation, 1474-1479
precautions during therapy with, 2497
principles of therapy with, 2496-2498
protein degradation and, 199
selection of, 2496, 2497t
side effects of long-term therapy with, 2497
single-dose
for myocardial protection, 270
withdrawal from, 2497
Stevens-Johnson syndrome
Kawasaki disease vs., 1549
Stewart Hamilton equation, 935
Still, George Frederick, 688t
Stillbirth(s)
in mothers of congenital heart disease patients, 676
Still's murmur, 688t, *1922*, 1922t, 1922-1923
Stimulation threshold
in pacing
defined, 2154
Stocking(s)
elastic
to prevent pulmonary embolism, 2510
Stokes-Adams syndrome, 1934
Straight back syndrome, 678, 694
electrocardiographic findings in, 726-727
pulmonary valve stenosis vs., 1396
Strauss method
for sinoatrial conduction time assessment, 1768-1770, *1769-1770*
Strawberry tongue
in Kawasaki disease, 1544, *1545*
Streptobacillus moniliformis
endocarditis due to, 1570
Streptococcal esterase, 1487
Streptococcus(-i). *See also* Pneumococcal infection; Streptococcus milleri
alpha-hemolytic, 1486
antibodies to
in rheumatic fever diagnosis, 1495
beta-hemolytic, 1486
endocarditis due to, 1569
beta-hemolytic group A, 1486-1487
antibodies to, 1487
extracellular products of, 1487
rheumatic fever and, 1485-1487
rheumatogenic strains of, 1488
classification of, 1486, 1568
dextran production by
infective endocarditis and, 1562
endocarditis due to, 1568-1569
treatment of, 1571-1572
epidemiology of infection with, 1487-1488
gamma, 1486
Kawasaki disease and, 1549
nutritionally deficient
culture techniques for, 2047-2048
pericarditis due to, 1591
structure of, *1486*, 1486
viridans, 1568
infective endocarditis due to, 1568
nutritionally variant, 1568
Streptococcus milleri, 1568
in brain abscess, 2465
Streptococcus pneumoniae. *See* Pneumococcal infection
Streptodornase, 1487
Streptokinase, 1487, 2082
effects on pulmonary circulation, 379
for myocardial protection, 271
in myocardial infarction management, 1718
Streptolysin O, 1487
Streptolysin S, 1487
Streptomycin, 2056
for infective endocarditis, 1571
Streptozyme test
in rheumatic fever diagnosis, 1495
Stress (mechanical). *See also* Wall stress
defined, 232
Stress (physiologic)
coronary artery disease and, 2281
Stridor
after extubation, 2254-2255
String galvanometer
Einthoven's, 510-511, *512*
Stroke. *See* Cerebrovascular accident(s)
Stroke volume
afterload and, 237-239, *238*
in fetus and newborn, 240, *241*
calculation of
from cine angiography, 496
contractility and, 238-239, *239*
defined, 231
determinants of, 231
in response to exercise, 430
preload and, 237, *238*
Student's t-test, 650-651
Stunning
myocardial, 266, 273-275, *275*
Stunting, 2355
Subaortic stenosis. *See* Aortic stenosis, subvalvular
idiopathic hypertrophic. *See* Hypertrophic cardiomyopathy
Subarachnoid hemorrhage
with coarctation of the aorta, 2311
Subcardinal vein(s), 100
Subclavian artery(-ies). *See* Left subclavian artery; Right subclavian artery
Subclavian flap technique
for coarctation repair, 1368, *1370*, 2216, *2217*
Subclavian lymphatic duct, 112
Subclavian steal syndrome
with Blalock-Taussig shunt, 1091, 2312
Subclavian vein
cannulation of
for monitoring during anesthesia, 2296
origin of, 99
Subcutaneous nodule(s)
in rheumatic fever, 1491, 1493
Subendocardial ischemia
during oxygen supply and demand mismatch, 261
electrocardiographic findings in, 742
in cardiac hypertrophy
contractility changes due to, 246-247
Subepicardial ischemia
electrocardiographic findings in, 742
Subpulmonic stenosis. *See* Pulmonary stenosis, subvalvular
Substance P, 362
Substrate utilization
nuclear magnetic resonance studies of, 615
Succinylcholine, 2295t, 2295, 2553t
for tracheal intubation, 2297
Sudden death, 674-675, 1912-1916
after tetralogy of Fallot repair
risk of, 2037
ventricular arrhythmias and, 1895
arrhythmias and, 675
in anomalous left coronary artery, 1457-1458
in aortic stenosis, 1342
possible mechanism of, 1336
in arrhythmogenic right ventricular dysplasia, 1639
in hypertrophic cardiomyopathy, 1634
ventricular arrhythmias and, 1892-1893
in mitral valve prolapse, 1982
in pulmonary valve stenosis, 1398
prevention of, 1915-1916
risk of
electrophysiology studies in evaluation of, 1744
Sudden infant death syndrome (SIDS), 342
cardiorespiratory autonomic control mechanisms in, 330
myocarditis and, 1582
prolonged Q-T interval and, 1889
sinus node dysfunction and, 1776
Sufentanil
hemodynamic effects of, 2294t
Suicide right ventricle
after pulmonary valvotomy, 1404
Sulcus terminalis, 113
Sulfadiazine
pyrimethamine with, 2060
Sulfamethoxazole
trimethoprim with. *See* Trimethoprim-sulfamethoxazole
Sulfasalazine
digoxin interaction with, 2363
Sulfhemoglobin
in acquired methemoglobinemia, 2336
Sulfinpyrazone
antiplatelet therapy with, 2081
Sulfonamide(s), 2059-2060. *See also* particular drugs
adverse effects of
in neonates, 2048
Superior vena cava, 1463-1464
anatomy of, 111-112
anomalies of, 1463-1465, *1466-1467*
echocardiographic detection of, 1466t
bilateral, 1464, *1466*
blood flow in
Doppler assessment of, *788*, 788
development of, 100
echocardiographic assessment of, 774-775, *775*, *780*
obstruction of
after intra-atrial baffle repair of transposition of the great arteries, 2040-2041, 2263
persistent left, 1464, *1466*
computed tomography assessment of, 883, *891*
connecting to left atrium, 1464-1465, *1467*
nuclear magnetic resonance imaging in, 860-861
with tricuspid atresia, 1119
right
connecting to left atrium, 1465
thrombosis of
computed tomography assessment of, 883, *890*
Superior vena cava syndrome
after Fontan procedure, 2262

Superoxide dismutase
effects on postischemic dysfunction, 274
for myocardial protection, 271
Superparamagnetism, 603-604, *604*
Supine hypotensive syndrome of pregnancy, 2375
Supplemental Security Income (SSI), 2529
Supracardinal vein(s), 100
Supraclavicular bruit, 1922t, *1923*, 1923-1924
Supravalvar mitral ring, 1309
cor triatriatum vs., 1308
Supravalvar stenosing ring of left atrium. *See* Supravalvar mitral ring
Supraventricular tachycardia, 1809-1848
age at onset of, 1810-1811, 1811t, *1811*
atrial activation sequence in, 1828-1830, *1829*, 1830t, *1831*
atrial automatic
mechanisms for termination of, 2167
atrial ectopic focus, 1843-1844, *1844-1845*
characteristics of, 1834t-1835t, 1846t
treatment of, 1844, 2176-2179, *2178-2179*, 2179t
atrial muscle reentry, 1759, 1760, *1761-1762*, 1836, *1837*
characteristics of, 1834t-1835t, 1846t
treatment of, 1836, 2159, 2167
atrioventricular node reentry, 1836-1837, *1838*
atypical. *See* Supraventricular tachycardia, junctional reciprocating, permanent
characteristics of, 1834t-1835t, 1846t
Lown-Ganong-Levine syndrome vs., 1841-1842
treatment of, 1837
bundle branch block with, 1830-1831, *1832*
ventricular tachycardia vs., 1874, 1881
clinical features of, 1810t-1813t, 1810-1813, 2546t
congestive heart failure and, 1812t, 1812-1813, 2011, 2012
defined, 1809, *1810*
diagnosis of
by electrophysiologic study, 1826-1832
echocardiographic, in fetus, 813-814, *814*, 815, *818*
differential diagnosis of, on surface electrocardiogram, 1818-1820, *1819-1821*
electrophysiology study of, 1747-1749, *1748*
indications for, 1826
technique of, 1826t, 1826-1832, *1827*
exercise electrocardiography in assessment of, 1740, *1741*
family history in, 1812
fetal, *1908-1910*, 1908-1910, 1910t
echocardiographic diagnosis of, 813-814, *814*, 815, *818*
management of, 817-818
His bundle reentry, 1835t, 1837
junctional ectopic focus tachycardia vs., 1844-1845
treatment of, 1837
in Lown-Ganong-Levine syndrome. *See under* Lown-Ganong-Levine syndrome
in Wolff-Parkinson-White syndrome. *See under* Wolff-Parkinson-White syndrome
incidence of, 1809
junctional automatic
sudden death and, 1913-1914
junctional ectopic focus, 1842-1843, 1844-1845, *1845-1846*
characteristics of, 1834t-1835t, 1846t
postoperative, 2258
treatment of, 1845
junctional reciprocating
fetal, 1910t
permanent, 1834t-1835t, 1842, *1843*, 1846t, 2176
Mahaim. *See under* Mahaim fiber(s)
mechanisms of
differentiating points in clinical estimation of, 1825-1826
P waves during, 1813, *1815*, 1816t
diagnostic significance of, 1846-1847
paroxysmal
in pregnancy, 2381
paroxysmal atrial
postoperative, 2258
P-QRS relationship in, 1813, *1816-1817*
predisposing factors for, 1811-1812, 1812t
preexcitation in, 1813, 1818t
QRS morphology during, 1813t, 1813, *1814*
reciprocating. *See also* Supraventricular tachycardia, junctional reciprocating
fetal, 1908, *1908-1909*, 1910t
recurrence of, 1816, 1818t, *1819*
reentry with bypass tract, 1837-1842, *1839*
reentry without bypass tract, 1832-1837
response of, to drugs
electrophysiologic studies in assessment of, 1831-1832
sinus node reentry, 1834-1836, *1836*
characteristics of, 1834t-1835t, 1846t
treatment of, 1834-1836
sudden death and, 1913-1914
syncope due to, 1937, *1939*
termination of, 2171
cardioversion for, 2171
mechanisms for, 2167
pacemaker for, 2156-2159, *2157-2158*
transesophageal pacing for, 2164-2167, *2165*
treatment of
emergency, 2546t
long-term, 1824t, 1824-1825
recommendations for, based on noninvasive assessment, 1820-1825
results of, 1814-1818, *1818-1819*
short-term, 1821t, 1821-1824
surgical, 2174-2179, 2176t, *2177-2179*, 2179t
types of, 1832-1845, 1834t
electrophysiologic criteria for diagnosis of, 1835t
noninvasive estimation of, 1845-1847, 1846t
surface electrocardiographic characteristics of, 1835t
with ectopic focus, 1842-1845. *See also* Supraventricular tachycardia, atrial ectopic focus; Supraventricular tachycardia, junctional ectopic focus
with myocardial infarction
management of, 1718
with unidirectional retrograde accessory pathway. *See* Kent bundle, concealed
Surfactant, 351
Surfactant replacement therapy
patent ductus arteriosus and, 2113
Surgery. *See also* Cardiac surgery; particular procedures and under particular disorders
anesthesia maintenance for
in congenital heart disease, 2298-2299
care after. *See* Postoperative care
complications of
defined, 2025
during chronic anticoagulant therapy, 2080-2081
for cardiac transplantation. *See* Cardiac transplantation
preparation for, 2290-2293
residua of
defined, 2024-2025
sequelae of
defined, 2025
thoracic
scoliosis and, 2450-2451
timing of, after stroke, 2308
Susceptibility testing, 1571, 2048
Sutton's disease, 2418
Swan-Ganz catheter(s). *See* Pulmonary artery catheter(s)
Sweating, 674
congestive heart failure and, 1007-1008
Swiss cheese septum, 1004
Sydenham's chorea, 1491, 1492, 1493
treatment of, 1499
Sympathectomy
left
for long Q-T syndrome, 342
Sympathetic efferent blocker(s)
effects on pulmonary circulation, 374t, 376
Sympathetic neuronal function
evaluation of, 333-335
Sympathomimetic drug(s)
effects on pulmonary circulation, 374t, 375
syncope due to, 1932
Syncope, 1929-1946. *See also* Near-syncope
benign, 1929-1930, 1931t
cardiac, 1930-1937
physical examination in diagnosis of, 1930, 1931t
primary, 1930-1932
secondary to arrhythmias, 1932-1937, *1933-1940*, 1936t
cardiovascular, 1929-1939
carotid sinus, 1938
causes of, 330
cerebrovascular, 1938-1939
characteristics of, 1929
classification of, 1929
cough (tussive), 1938
defined, 1929
differential diagnosis of, 1942t
evaluation of, 1941-1945, 1944t
electrophysiology studies in, 1743-1744
laboratory examination in, 1941-1945
quantitative autonomic nervous system evaluation in, 1943-1945
noncardiovascular, 1939-1941
orthostatic, 1937-1938
post-micturition, 1938-1939
quinidine, 1941
seizure vs., 1941, 2322
seizures with, 1726
sudden death and, 675
vagovagal, 1938
vascular, 1937-1939, *1940*
vasodepressor, 1929-1930, 1931t
vasovagal, 1929-1930, 1931t
Syncytiotrophoblast, 72
Synergism
in antimicrobial therapy, 2050
Systemic lupus erythematosus, 1529-1532
atherosclerosis in, 1993
cardiovascular manifestations of, 1530-1532
congestive heart failure due to, 2015
criteria for diagnosis and classification of, 1529t, 1529-1530
drug-induced, 1532-1533, 1533t, 2090
electrocardiographic findings in, 754
maternal

congenital complete atrioventricular block and, 676t, 676, 1908
Systemic vascular resistance. *See also* Vascular resistance
changes in
in pregnancy, 2375
in response to exercise, 430-431
magnitude of left-to-right shunt and, 1001
normal values for, 932
units used in measurement of, 932-933
Systemic venous return
anomalies of, 1462-1470
multiple, 1469
nonsurgical treatment of, 1469
nuclear magnetic resonance imaging in, 860-861
radionuclide tracer flow analysis in detection of, 846
surgical significance of, 1469
embryology of, 1462-1463, 1463t, *1464-1465*
normal, *1463*
Systemic-to-pulmonary artery shunt. *See* Shunt(s), palliative; particular procedures
Systolic anterior motion of anterior mitral leaflet
in hypertrophic cardiomyopathy, 1627, 1629, 1630, *1631*, 1632
Systolic click. *See also* Midsystolic click
with ventricular septal aneurysm, 687
Systolic click murmur syndrome. *See* Mitral valve prolapse
Systolic click syndrome. *See* Mitral valve prolapse
Systolic ejection period
in aortic valve area calculation, 942t, 943
Systolic ejection time
in aortic valve area calculation, 942t, 943
Systolic pressure-rate index, 253t, 253
Systolic pressure-time index (SPTI), 253
left ventricular oxygen requirement estimation from, 1336
Systolic reserve
of fetal heart, 284
Systolic time interval(s)
in myocardial infarction, 1708-1709

T artifact
in ventricular septal defect, 1010
T lymphocyte(s)
activation of
cyclosporine's effects on, 2243, *2243-2244*
classification of, 2241
in B lymphocyte activation, 2240
in cellular immunity, 2241
in myocarditis pathogenesis, 1579-1580, *1581*
origin of, 2239-2240, *2240*
T tubule(s)
electron microscopic features of, 130
T wave(s), 720-721, *721*
benign changes in, 742
functional changes in, 741-742
hyperacute, 745, 1700, *1702*
P wave vs., 722, *723*
primary changes in, 741
secondary changes in, 741
U wave vs., 721-722, *722-723*
T wave alternans, 1879
T1 relaxation time. *See under* Nuclear magnetic resonance
T2 relaxation time. *See under* Nuclear magnetic resonance
Tachycardia. *See also* Atrial flutter; Sinus tachycardia; Supraventricular tachycardia; Ventricular tachycardia
bidirectional
in digitalis toxicity, *750*, 750
coronary vascular reserve in, 263
criterion for, 680
differential diagnosis of, 2546t
fetal, *1908-1910*, 1908-1910, 1910t
defined, 1905
pacemaker-mediated
defined, 2153
pacing for, 2156-2161
postoperative, 2258
symptoms of, 1726
wide QRS
differential diagnosis of, 1820, *1821*
Tachycardia-bradycardia syndrome, 1853
pacemaker in management of, 1858
Tachypnea, 673
transient, of newborn. *See* Transient tachypnea of newborn
Takayasu's arteritis, 975-976, *976*
abdominal coarctation in, *982*, *1365*, 1366
renal vascular hypertension due to, 985
Tamponade. *See* Cardiac tamponade
Tandem repeats
defined, 63
Tangier disease, 481
Tantalum-178, 564, 848
first-pass blood pool imaging with, 840
Tape drive(s), 658
TAR syndrome, 2329t, 2330, *2405*, 2405
congenital heart disease in, 678t
orthopedic problems in, 2457
TATA box, 16, 18
defined, 62
Taussig, Helen B.
on causation of congenital heart disease, 139
Taussig-Bing malformation, 1213, 1215. *See also* Double-outlet right ventricle
surgery for, 1229
decisions and techniques for, 2220
transposition physiology in, 1177
Tay-Sachs disease, 1663
Tazicef. *See* Ceftazidime
TE
defined, 618
Teacher
physical education
role in cardiac rehabilitation program, 2268
Technetium-99m, 564
first-pass radionuclide angiocardiography tracer flow analysis using, 846
radioactive decay of, 561
red blood cell labeling with, 837
Technetium-99m pertechnetate
first-pass blood pool imaging with, 840
Technetium-99m-isonitrile compound(s), 849
Technetium-99m-labeled macroaggregated albumin, 564
vascular perfusion imaging using, 847
Technetium-99m-labeled pyrophosphate, 564, 845
imaging with. *See* Myocardial scintigraphy, infarct-avid
Teflurane
effects on electrocardiogram, 751
Teichoic acid antibody
in infective endocarditis, 1565
Telemetry
in pacing, 2144, 2149
defined, 2154
real-time, 2153-2154
self-monitoring
with antitachycardia pacing, *2160*, 2160
Television camera(s)
in digital subtraction angiography system, 639
Temperature
body. *See* Body temperature
of cardiac catheterization laboratory, 948
of neonatal environment, 2480-2481
of operating room, 2293
for neonate, 2481
Tendon(s)
false
in left ventricle, 119
Tendon of Todaro, 111, 113
Tensilon. *See* Edrophonium
Tension
defined, 232
Tension-time index (TTI), 253t, 253
Teratogen(s), 676t. *See also* particular teratogens
syndromes due to environmental exposures
hematologic and oncologic problems with, 2330
Teratology, 152-170
Teratoma, 1652
Terbutaline
effects on pulmonary circulation, 374t, 375
in myocardial infarction management, 1717
Tesla
defined, 618
Test(s)
diagnostic
characteristics of, 142-144, *143-144*
Tet spell(s). *See* Tetralogy spell(s)
Tetracycline(s)
adverse effects of, 2048
in liver disease, 2049
in renal failure, 2049
for Lyme disease, 1538
Tetralogy of Fallot, 1073-1100
acyanotic (pink)
management of, 1967
physiology of, 1071
anatomic considerations in, 1073-1077, *1074-1076*
angiocardiography in, 958t, 1085-1087, *1086-1088*
anomalies associated with, 1077
anomalous right subclavian artery with, 1428, 1439
atrioventricular canal defect with, 1076
repair of, 1049
auscultatory findings in, 1080-1081
body surface map findings in, 519
cardiac catheterization in, 1085-1088
clinical features of, 1080-1081
postoperative, 1081
computed tomography assessment of, *896*, 903
coronary artery anomalies with, 970-971, 971t, 1458
echocardiographic assessment of, 776
digital subtraction angiography in, *909*
double-outlet right ventricle vs., 1215
echocardiographic findings in, 1082-1085, *1083-1084*
in fetus, 810-811
electrocardiographic findings in, 1081
electrophysiologic studies of
postoperative, 1087-1088
embryology of, 1077-1078
epidemiology and genetics of, 1078
management of, 1088-1097. *See also* Tetralogy of Fallot, surgical treatment of

Tetralogy of Fallot, management of *(cont.)*
interventional catheterization procedures in, 1088
medical, 1088-1090
murmur in, 688, 1080-1081
natural history of, 1088
neurologic complications of, 1089
nuclear magnetic resonance imaging in, 859, *860-861*
physiology and hemodynamics of, 1078-1080
pregnancy with, 2380
pulmonary valve stenosis vs., 1386, 1397
radiographic findings in, 703, *704-705*, *1081*, 1081-1082
recurrence risk for, 176t
squatting in, 673, 1079
surgical treatment of, 1090-1094, 2036
arrhythmias after, 1097, 1894-1896
clinical caveats for, 2299t
clinical features after, 1081
complete repair, 1092, *1093*
complications of, 2038, 2262
decisions and techniques for, 2213
electrophysiologic studies after, 1087-1088
late results of, 1094-1097
palliative, 1090-1092, *1091*
patient selection for, 2038-2039
primary repair vs. palliation, 1092
pulmonary hypertension after, 1085
residua of, 2036
right ventricular dysfunction after, 843
sequelae of, 2036-2038, *2037-2038*
ventricular late potentials as predictors of arrhythmias after, 521
unoperated
ventricular arrhythmias with, 1891
ventriculoarterial connection in, 772-773
with pulmonary atresia
anatomic considerations in, 1074-1077, *1075*
angiocardiography in, 1086-1087, *1088*
echocardiographic findings in, 1084-1085
late results of repair of, 1094-1097
physiology and hemodynamics of, 1079
pulmonary blood flow in, 1074-1076, *1075*
repair of, 1094, 1964
Tetralogy spell(s), 672-673, 1071-1072
breath-holding vs., 2323
in pulmonary vascular disease, 1997
therapeutic considerations in, 1997-1998
intraoperative, 2298
management of, 1089-1090, 2545t
physiology of, 1079-1080
syncope in, 1931-1932
Tetrodotoxin
effect on delayed afterdepolarizations, 315
Thalassemia(s), 1670, *2332*, 2332-2334, 2333t-2334t
Thalidomide
maternal exposure to
congenital heart disease and, 676t, 678t
Thallium-201, 564, 843
imaging with. *See* Myocardial scintigraphy, perfusion
radioactive decay of, 561
THAM. *See* Tromethamine
Thebesian valve, 112-113
formation of, 84
Thebesian vein(s), 113, 117, 126
Theophylline
adverse cardiac effects of, 2506
for cor pulmonale, 2505
for myocardial infarction, 1717
for sinus node dysfunction, 1779
inotropic effects of, 2068
patent ductus arteriosus and, 2113
Therapeutic(s), 2045-2273. *See also* particular treatment modalities
Thermodilution
blood flow measurement by, 496
cardiac output determination by, 939-940, *940*
shunt measurement by, 940
Thermogenesis
nonshivering, 2480
Thiamine deficiency, 1666-1667
cardiac failure in
response to drugs in, 2363
Thiazide(s). *See under* Diuretic(s); particular drugs
Thick filament(s), 130, *131*, 212, *212-213*, 213, 2065-2066, *2066*
Thin filament(s), 130, *131*, 212, *212-213*, 213-214, 2065-2066, *2066*
Thiocyanate toxicity
with nitroprusside, 2088-2089
Thiopental
hemodynamic effects of, 2294t
Thiosulfate
for cyanide toxicity, 2088
Thiourea drug(s)
for hyperthyroidism, 2492
Third factor. *See* Atrial natriuretic factor
Thirst, 459-460
Thoracic duct, 112
ligation of
for chylothorax, 2513-2514
Thoracic vein
origin of, 100
Thoracotomy
problems with incision for, 2029
Thorax. *See* Chest wall
Thorazine. *See* Chlorpromazine
3 sign
in coarctation of the aorta, 703, *1360*, 1360
Threshold potential, 296, *297*
Thrill, 683-684
Thrombocytopenia
after cardiopulmonary bypass, 2344
surgical bleeding due to, 2343
drugs causing, 2343t
Thrombocytopenia-absent radii syndrome. *See* TAR syndrome
Thromboembolism. *See* Embolism
Thrombolytic agent(s), 2082. *See also* Streptokinase
effects on pulmonary circulation, 379
for myocardial protection, 271
hemostatic tests for monitoring of therapy with, 2082t
in myocardial infarction management, 1718
Thrombomodulin
antithrombotic action of, 486
Thrombophlebitis
during pregnancy, 2383
Thrombosis
aortic
in neonate, 2488-2489
arterial, 2083-2084
in neonate, 2488-2489
postcatheterization, 2451-2453, *2453*
arterial endothelium's effects on, 486
atherosclerosis and, 488
cardiac
computed tomography assessment of, 903
cerebral, 2453-2454
in tetralogy of Fallot, 1089
in transposition of the great arteries, 1201-1202
in ventricular aneurysm
after myocardial infarction, 2283
mural
with cardiovascular catheter, 2462
postcatheterization
orthopedic sequelae of, 2451-2453, *2453*
slow flowing blood vs.
on nuclear magnetic resonance images, 600
venous, 2083
during pregnancy, 2383
with prosthetic valves, 2344
Thromboxane
in regulation of ductus arteriosus closure, 2112
Thumb abnormalities
congenital heart disease with, 678t, 678-679
Thumbprinting of intestine, 2359
Thymic wave sign, 692
Thymine
uracil vs., 14
Thymus
absence of
with interrupted aortic arch, 1377
on chest radiographs of normal infant, 692
Thyroid gland, 2491. *See also* Hyperthyroidism; Hypothyroidism
disease of
cardiac findings and management in, 2491-2494
in Down syndrome, 2498
in Turner's syndrome, 2498
function of
evaluation of, in seriously ill patient, 2493, 2494t
Thyroid hormone(s). *See also* Thyroxine; Triiodothyronine
actin and, 39
cardiac metabolism and, 199
isomyosin changes in response to, 37, *37-38*
postnatal cardiac output increase and, 287
Thyroid-binding globulin deficiency, 2493t
Thyroiditis
subacute, 2491
Thyrotropin-releasing factor stimulation test, 2492
Thyroxine (T_4), 2491. *See also* Thyroid hormone(s)
myosin isozyme form and, 219
TI (inversion time)
defined, 618
Ticarcillin, 2053
aminoglycoside synergism with, 2056
amiodarone interaction with, 2052
clavulanic acid with (Timentin), 2053
digoxin interaction with, 2052
dosage adjustment for renal insufficiency, 2440t
parenteral dosage for severe infection, 2057t
Ticlopidine
antiplatelet therapy with, 2082
Tidal volume, 353
in response to exercise, 431
Tietze's syndrome, 1948
Time constant
for respiratory unit, 353
Timentin (ticarcillin/clavulanic acid), 2053
Time-of-flight phenomenon, *599*, 599
blood flow measurement using, 602
Timolol
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2365
Tissue-type plasminogen activator

thrombolytic therapy with, 2082
Titratable acid, 461
Tobacco. *See* Smoking
Tobramycin, 2056-2057
dosage adjustment for renal insufficiency, 2440t
parenteral dosage for severe infection, 2057t
Tocainide, 2130, 2550t
dosage adjustment for renal insufficiency, 2441t
effects on electrocardiogram, 751
for ventricular arrhythmias, 1898-1899
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2365
Todd's postictal paralysis
stroke vs., 2306
Tofranil (imipramine)
effects on electrocardiogram, 752
Tolazoline (Priscoline), 2549t
effects on pulmonary circulation, 373-375, 374t
in determining reversibility of pulmonary hypertension, 932
in persistent pulmonary hypertension management in neonate, 2486
Tonsillectomy
for rheumatic fever prophylaxis, 1499
Topical magnetic resonance
spatial localization of nuclear magnetic resonance spectra with, 613
Torque
defined, 618
Torsades-de-pointes tachycardia. *See under* Ventricular tachycardia
Total anomalous pulmonary venous connection, 1154-1167
anatomy of, 1154-1156, *1155*
angiographic assessment of, 958t, 1162
atrial septal defect with, 1026
atrioventricular canal defect with, 1045
cardiac anomalies associated with, 1156-1157
cardiac catheterization in, 1161-1162, *1162*
cardiac type (type 2), 1154-1156, *1155*
repair of, 1164, *1166*
clinical features of, 1158-1159
defined, 1145
diagnostic techniques for, 1159-1162
differential diagnosis of, 1162
echocardiographic assessment of, 775, 1159-1160, *1160-1161*
embryology of, *1147*, 1147
genetics and epidemiology of, 1154
infracardiac (infradiaphragmatic) type (type 3), *1155*, 1156
radiographic findings in, 697, *702*
repair of, 1164
mixed type (type 4), 1156
myocardial infarction in, 1706-1707
natural history of, 1162-1163, *1163*
nonobstructed
management of, 1163, 1967
nuclear magnetic resonance imaging in, 861-862
obstructed
clinical features of, *1158*, 1158-1159
congestive heart failure due to, 2012
management of, 1163, 1963
natural history of, *1163*, 1163
pathophysiology of, 1157
pathophysiology of, 1157-1158
prenatal diagnosis of, 1167
radiographic diagnosis of, 697, *702*
in newborn, 696
radionuclide angiographic findings in, 1160-1161
supracardiac type (type 1), 1154, *1155*
radiographic findings in, 697, *702*
repair of, 1164, *1165*
treatment of, 1163-1164, *1165-1166*, 1963, 1967
long-term results, 1164-1167, *1167*
types of, 1154-1156, *1155*
with nonrestrictive interatrial communication
clinical features of, 1159
natural history of, 1163
pathophysiology of, 1158
with restrictive interatrial communication
clinical features of, *1159*, 1159
natural history of, 1163
pathophysiology of, 1157-1158
Total lung capacity, 353
Toxic shock syndrome, 2469-2470
Toxoplasma gondii infection
after heart transplantation, 2245, 2468
cardiac manifestations of, 2471
TR (repetition time)
defined, 618
Trabecula(e) carna(e)
of left ventricle, 119
of right ventricle, 114-115
Trabecula septomarginalis, 115-116
in double-outlet right ventricle, *1214*, 1214
Trabecular pouch, 1248
Tracer(s)
diffusible
blood flow measurement using, 256, 495, 622
in positron emission tomography, 620-621
Tracer flow analysis
first-pass radionuclide angiocardiography for, 845-846, *846-847*
Trachea
malformations of
with anomalous left pulmonary artery, 1430
Tracheomalacia
anomalous innominate artery and, 1444
Tracking, 2152, 2154
Transannular outflow patch
in tetralogy of Fallot repair, *1093*, 1093-1094
Transcription, 14
defined, 63
protein binding's effects on, 16
reverse, 7
Transcutaneous P_{O2} monitoring
limitations of, 2483, 2485
Transducing mechanism, 319
β-Transforming growth factor (TGFβ), 31
Transfusion(s)
complications of, 2298
during open heart surgery, 2298
fear of AIDS and, 2260-2261
for DiGeorge anomaly patients, 2409
in thalassemia management, 2332-2333
neocyte
in thalassemia management, 2332-2333
postoperative bleeding due to, 2260
Transient tachypnea of newborn, 695-696
total anomalous pulmonary venous return vs., 697
Transition
defined, 13
Transition lead(s)
R and S wave amplitude in, 720
Translation
defined, 63
Translocation, *14*, 14, 177
Transmitter
defined, 618
Transmitter coil
defined, 619
Transmutation, 561
Transplantation
bone marrow. *See* Bone marrow transplantation
cardiac. *See* Cardiac transplantation
human leukocyte antigens in, 2241
liver
angiography in assessment for, 981
renal
angiography in assessment for, *987*, 987
Transposition of the great arteries, 1175-1212
anatomic classification of, 1178-1179
anatomic considerations in, 1175-1178, *1176-1177*
angiocardiographic assessment of, 959t, 1193-1195, *1194-1195*
atrial septostomy for, 1195-1199, *1196*, *1198-1200*
results of, 1202
cardiac catheterization in, 1188-1195
diagnostic, 1192-1195
postoperative indications for, 1190
preoperative indications for, 1188-1190
clinical features of, 1182
complex, 1179
clinical features of, 1182
physiology of, 1181-1182
Rastelli operation for, 1207-1209, *1208*
coronary artery anomalies in, 971, 1458-1459, *1459*
"corrected". *See also under* Ventricular inversion
coronary artery anomalies in, 971, *1459*, 1459
defined, 1281
radiographic findings in, 703, *704*
defined, 1175-1176, 1281
echocardiographic findings in, *772*, 772, 1183-1188, *1184-1189*
electrocardiographic findings in, 1182-1183
electrophysiologic studies in, 1195
embryology of, 1179-1180
epidemiology and genetics of, 1180
hypoxia and polycythemia in, 1201
infundibular morphology in, 1179
major complicating lesions with, *1177*, 1177-1178
management of, 1199-1209. *See also* Transposition of the great arteries, surgery for; particular procedures
history of, 1200t
prostaglandin therapy in, 2119
natural history of
modification of, by therapy, 1199-1201
neurologic complications of, 1201-1202
nuclear magnetic resonance imaging in, 860
partial. *See* Double-outlet right ventricle
patent ductus arteriosus with, 1060, 1178
physiology and hemodynamics of, 1180-1182, *1181*
pulmonary vascular obstructive disease in, 1202
radiographic findings in, 703, *704*, *1183*, 1183
relationship of great arteries in, 1178-1179
shunt quantitation in, 923-924, *924*
surgery for, 2039. *See also* particular procedures
arterial switch repair, 1206-1207, *1207*
atrial baffle procedures, 1203-1206, *1204*, 2263
clinical caveats for, 2299t

Transposition of the great arteries, surgery for *(cont.)*
complications of, 2041
decisions and techniques for, 2213-2215, *2214-2215*
palliative, 1203
Rastelli operation, 1207-1209, *1208*
residua of, *2039-2040*, 2039-2040
sequelae of, *2039*, 2040-2041
sinus node dysfunction after, 1776
with intact ventricular septum
management of, 1961-1962
physiology and hemodynamics of, 1180-1181
with ventricular septal defect, *1177*, 1177-1178
management of, 1967
physiology and hemodynamics of, 1181
Transposition physiology, 1173-1174
adequacy of mixing in, 1174
clinical setting of, 1173-1174
Transverse magnetization
defined, 619
Transverse sinus of pericardium, 110
Transversion
defined, 13
Traube's sign. *See* Pulsus alternans
Trauma, 2534-2540
aortic, 2537
computed tomography in assessment of, 883-897, *894*
thoracic aortography in management of, 978, *980*
blunt chest, myocardial infarction after, *1709*, 1713
cardiac
nonpenetrating, 2534-2537
penetrating, 2537-2539
chest pain due to, 1948
coronary artery
blunt, 2537
penetrating, 2538
head
hyperadrenergic dysautonomia due to, 338
pelvic
angiography in assessment of, 988-992, *991*
pericardial
blunt, 2537
penetrating, 2538
renal
angiography in management of, 987-988
to extremities
angiography in assessment of, 990-992, *991*
to valves, 2536, 2538
Travel, air, 448
Treacher Collins syndrome, 2401-2402, *2402*
Treadmill. *See also* Exercise testing
exercise testing with, 829, 830t, 830
Treppe response, 207
sodium-calcium exchanger in, 205
Triamterene, 2105
cimetidine interaction with, 2367
dosage adjustment for renal insufficiency, 2441t
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2366
Triangle of dysplasia
in arrhythmogenic right ventricular dysplasia, 1639
Tricarboxylic acid cycle, *196*, 196
Trichinella spp.
myocarditis due to, 1582, 2471
Trichinosis, 2471
Trichloroethylene
effects on electrocardiogram, 751
Tricuspid atresia, 1118-1126
angiographic views for, 959t
atrial flutter and, 1853
cardiac catheterization in, 1122-1123
classification of, 1118t, 1118
clinical history of, 1120-1121
conduction system in, 1253, *1254*
echocardiographic findings in, 1122
electrocardiographic findings in, 1121-1122, *1122*
hemodynamics in, *1120*, 1120
management of, 1123-1125, *1124*
clinical caveats for surgery, 2299t
surgical decisions and techniques for, 2217
nuclear magnetic resonance imaging in, 860
pathology of, 1118-1120, *1119*
physical examination in, 1121
radiographic findings in, 1122
single ventricle and, 1251
Tricuspid commissurotomy
for rheumatic tricuspid stenosis, 1523
Tricuspid insufficiency
after surgery for transposition of the great arteries, 1205-1206, *2040*, 2040, 2263
after tetralogy of Fallot repair, 1081
after ventricular septal defect repair, 2030
congestive heart failure due to, 2012
diagnosis of
in fetus, *821-822*
functional
in rheumatic heart disease, 1518
in hypoplastic left heart syndrome, 1327
rheumatic
cardiac catheterization and angiography in, 1520
clinical manifestations of, 1518-1520
pathology of, 1518
pathophysiology of, 1518
surgery for, 1523
ventricular inversion with
hemodynamics and physiology of, 1241
Tricuspid stenosis
balloon dilation for, 2194-2195
rheumatic
cardiac catheterization and angiography in, *1520*, 1520
clinical manifestations of, 1518-1520
pathology of, 1518
pathophysiology of, 1518
surgery for, 1523
Tricuspid valve
abnormalities of
ventricular inversion with, 1237
anatomy of, *113*, 114
balloon dilation of, 2194-2195
blood flow across
Doppler assessment of, 788-789, *789*
Doppler quantitation of, 795
quantitation of, 943
velocity of, in fetus, 821
Ebstein's anomaly of. *See* Ebstein's anomaly
echocardiographic assessment of, 774, *780*
in fetus, 807, 808
formation of, 89
identifying features of, 1233
on echocardiography, 1242
in atrioventricular canal defects, 1037, 1038
in pulmonary valve atresia with intact ventricular septum, 1109-1110
reconstruction of
for rheumatic tricuspid incompetence, 1523
rheumatic disease of, 1518-1520
trauma to, 2536
Tricyclic antidepressant(s)
effects on electrocardiogram, 751-752
hypoadrenergic dysautonomia due to, 340
Trifascicular block, 737, *1794*, 1794-1795, 1795t
Trigeminy, 1956
ventricular, 1872-1874, *1873*
Triggered activity, 314-316
Triggered mode
in pacing
defined, 2154
Triglyceride(s), 475-476. *See also* Hypertriglyceridemia
medium-chain
in chylothorax management, 2513
in nutritional therapy, 2357
metabolism of, 195, 477-478
plasma levels of
atherosclerosis and, 481
Triiodothyronine (T_3), 2491. *See also* Thyroid hormone(s)
postnatal cardiac output changes and, 241
Trilogy of Fallot, 1070
Trimethadione
maternal exposure to
congenital heart disease and, 676t
Trimethoprim-sulfamethoxazole (Bactrim; Septra), 2059-2060
parenteral dosage for severe infection, 2057t
Triple primer sequencing method, 26-27, *27*
Triple product, 253t, 253
Tris (hydroxymethyl) aminomethane. *See* Tromethamine
Trisomy, 176
Trisomy 4p, 2429t
Trisomy 8, 184-185
Trisomy 9, 185
Trisomy 9 mosaic, 185, 2429t
Trisomy 9p, 2429t
Trisomy 10p, 185
Trisomy 11;22, 187-188
Trisomy 13, 182-183, *183*, 2429t
congenital heart disease in, 677t-678t, 678
hand abnormalities in, 679
hematologic and oncologic problems with, 2328, 2329t
renal anomalies in, 2429t
Trisomy 18, 181-182
congenital heart disease in, 677t-678t, 2429t
hand abnormalities in, 679
hematologic and oncologic problems with, 2328, 2329t
renal anomalies in, 2429t
Trisomy 21. *See* Down syndrome
Tromethamine (THAM), 2553t
for metabolic acidosis with cardiac arrest, 417
Trophoblast, 72
Tropomyosin, 40, *213*, 214, *2066*, 2066
developmental aspects of, 219
isoforms of, 40, 218
troponin interaction with, 214
Troponin, 40, *213*, 214, 2066, *2066*
developmental aspects of, 219
in actomyosin complex regulation, 215-216
isoforms of, 40, 218
tropomyosin interaction with, 214
Truncation error, 609
Truncus arteriosus (congenital anomaly), 1127-1133
abnormalities associated with, 1128-1129
anatomy of, 1127-1129

angiographic assessment of, 960t, *1130-1131*, 1130-1131
cardiac catheterization findings in, 1130
classification of, 1127-1128, *1128*
clinical features of, 1129
coronary artery anomalies with, 1128-1129, 1460
echocardiographic assessment of, 772, 1129-1130, *1130*
embryology of, 1127
neural crest injury and, 162
patent ductus arteriosus vs., 1064-1065
pathophysiology of, 1129
radiographic findings in, 697-703, *702*
treatment of, 1131-1132, 1965, 2215-2216, *2216*
with coronary ostia stenosis
myocardial infarction in, 1713
Truncus arteriosus (fetal structure), 81, 88
Trypanosomiasis
American, 2472
myocarditis due to, 1582
Tuberculosis
drug therapy of, 2060
pericarditis in. *See under* Mycobacterium tuberculosis
Tuberous sclerosis, 2400-2401, *2402*, 2430t
hematologic and oncologic problems with, 2329t
renal anomalies in, 2430t
rhabdomyoma and, 1650-1651
D-Tubocurarine, 2295t
Tubuloglomerular feedback system
in renal blood flow autoregulation, 451
Tumor(s). *See also* particular tumors
cardiac, 1647-1655, 2338
clinical manifestations of, 1647-1648
computed tomography assessment of, *902*, 903
diagnosis of, in utero, 1649
embolic events with, 1648
malignant, 1653-1654
physical examination and laboratory studies in, 1648-1650, *1649-1652*
prevalence of, 1647
systemic manifestations of, 1648
tachycardia and syncope due to, 1937, *1940*
therapy for, 1654
ventricular arrhythmias with, 1892, 1899-1900
hepatic
angiographic assessment of, 981, *983*
malignant. *See* Malignancy(-ies); particular tumors
nuclear magnetic resonance imaging of, *863*, 863
of extremities
angiography in assessment and management of, 992
pelvic
angiography in assessment and management of, 992
pericardial, 2338
renal
angiographic assessment of, 988, *989*
Tumor plop
in left atrial myxoma, 1511
Tunica adventitia
of arteries, 121, *122*
Tunica intima
of arteries, 121, *122*
of coronary arteries, 126, *127*
Tunica media
of arteries, 121, *122*
of veins, 112
Tuning
in nuclear magnetic resonance
defined, 619
Turbulence, 536-537, 598
murmurs and, 1919-1920
Turner's syndrome, *188-189*, 188-189, 677t-678t, 679, 2429t
coarctation of the aorta and, 1357
endocrine abnormalities in, 2498t, 2498
hematologic and oncologic problems with, 2329
hypoplastic left heart syndrome and, 1318
male. *See* Noonan's syndrome
orthopedic problems in, 2456
renal anomalies in, 2429t
Type A behavior
atherosclerosis and, 1992
Typhoid fever, 2469
Tyramine
alpha-adrenergic receptor responsiveness evaluation using, 334
response to, in syncope diagnosis, 1944-1945

U wave, 721, *722*
identification of, 1878
P wave vs., 722
prominent
causes of, 747
T wave vs., 721-722, *722-723*
Uhl's anomaly, 1893
arrhythmogenic right ventricular dysplasia and, 1637
Ebstein's anomaly vs., 1135
Ulcerative colitis
ankylosing spondylitis and, 1536
pharmacokinetics of beta blockers in, 2365
Ulnar nerve injury
due to cardiac surgery, 2313
Ultracef (cefadroxil), 2054
Ultrasound. *See also* Echocardiography
adverse effects of, 825
attenuation of, *527*, 527
in various media, 525t
backscatter of, 535-536
beam characteristics in, *527*, 527
Doppler. *See* Doppler echocardiography; Doppler ultrasound
imaging with
principles of, 768-769
intensity of, 527-528, *528*
obstetric. *See also* Echocardiography, fetal
initial examination, 806-807
physical properties of, in various media, 525t
physics of, 524-528, *525-528*, 768-769
pulsed, *526*, 526
reflection of, 525, *526*
resolution in, *527*, 527
safety of, 527-528, 781
scattering of, 525, *526*
tissue characterization by, 531
transmission of, 525-526
velocity of, in tissue, 768
wave characteristics of, 524-525, *525*
Umbilical artery
cannulation of, 951
arterial thrombosis after, 2488
for peripheral vascular angiography, 973
renal vascular hypertension and, 986
flow in
Doppler assessment of, 822, *824-825*
regulation of, 282
morphologic changes in, after birth, 132
Umbilical vein, 99
cannulation of
technique for, 949-950
cardiac catheterization via, 1191
flow in
Doppler assessment of, 822, *824*
regulation of, 282
morphologic changes in, after birth, 132
Undersensing
in pacing, 2159
defined, 2154
UNIX, 660
"Upstairs-downstairs" heart, *1240*, 1240
Uracil
thymine vs., 14
Urea, 2106
Uremic myocardiopathy, 2431-2432
Uric acid
atherosclerosis and, 1992
Uridine monophosphate, 14
Uridine triphosphate
in glycogen synthesis, 192
Urinary tract infection(s)
after heart transplantation, 2468
Urine
acidification of
buffering systems and, 462
factors affecting, 462t
concentration of, 454-456, *455*, 456t
in neonate, 465
dilution of, 456
Urine output
monitoring of, during anesthesia, 2297
postoperative, 2255
Urine water volume
daily obligatory, 456t, 456
Urokinase, 2082
effects on pulmonary circulation, 379
Usurpation
rhythms of, 1757
Uterine blood flow
fetal regulation of, 281-282
maternal regulation of, 281

V max, 296-297
VACTERL association, 678, 2411t, 2411
Vacuum tube amplifier(s)
in electrocardiography, 511-512
Vagal maneuver(s)
in supraventricular tachycardia treatment, 1821
Vagal sensory reflex(es)
pulmonary
characteristics of, 353t
Vagotonia
syncope due to, 1938, *1940*
Validity
in epidemiologic studies, 148
Valium. *See* Diazepam
Valsalva maneuver
eliciting, in infants, 1821
in baroreflex evaluation, *332*, 332-333
quantitative
in syncope diagnosis, 1944
Valsalva ratio, 333
Valve(s)
arterial
formation of, 89-90, *93*
cardiac. *See also* particular valves

Valve(s), cardiac *(cont.)*
calculation of area of, 940-944, 941t-943t, *941-943*
dilation of. *See* Balloon valvuloplasty
Doppler estimation of area of, *799*, 799
prosthetic. *See* Prosthetic valve(s)
replacement of. *See* Valve replacement
trauma to, 2536, 2538
venous, 112
origin of, 84, 85
Valve replacement. *See also* Prosthetic valve(s)
aortic
in aortic valvular stenosis, 1343
ventricular arrhythmias after, 1896
during pregnancy, 2379
for infective endocarditis, 1573
for rheumatic heart disease, 1521-1524
problems with, 1523t, 1523-1524
mitral, 1313-1314
Valvular heart disease. *See also* particular lesions
in juvenile rheumatoid arthritis, 1529
thromboembolism in, 2084
vasodilators for, *2093*, 2093
Valvular insufficiency. *See also* Aortic insufficiency; Mitral insufficiency; Pulmonary insufficiency; Tricuspid insufficiency
indicator dilution method for detection of, 938
nuclear magnetic resonance imaging in, 863
Valvular stenosis. *See also* Aortic stenosis; Mitral stenosis; Pulmonary valve stenosis; Tricuspid stenosis
nuclear magnetic resonance imaging in, 863
Valvulitis
in rheumatic fever, 1492-1493
Valvuloplasty
balloon. *See* Balloon valvuloplasty
Valvuloplasty and Angioplasty of Congenital Anomalies registry, 2188
Vancomycin, 2058-2059
aminoglycoside synergism with, 2056
dosage adjustment for renal insufficiency, 2440t
for infective endocarditis, 1571, 1572
gentamicin synergism with, 2058
parenteral dosage for severe infection, 2057t
prophylactic use of
for oral procedure in patient on chronic prophylaxis, 2050-2051
rifampin synergism with, 2058
toxicity of, 2049
Van't Hoff's law, 273
Variance, 649
analysis of (ANOVA), 651-652
Varicella
myocarditis due to, 1579
prevention of, in immunocompromised child, 2473
Varicella-zoster immunoglobulin
for immunocompromised child, 2473
Varicella-zoster virus infection
after heart transplantation, 2468
Vasa recta
urine concentration in, 455
Vascular impedance, 224, 235-236
Vascular perfusion imaging, 847, *848*
Vascular resistance, *932*. *See also* Pulmonary vascular resistance; Systemic vascular resistance
afterload and, 224, 236
calculation of
in cardiac catheterization, 929-933
formulae for, 931, 931t
measurement of, 236
placental. *See under* Placenta
units used in measurement of, 932-933
Vascular ring(s), 2508-2509
cardiac catheterization and angiography in, 1438-1439
complete, 2509
course, treatment and prognosis with, 1439-1450, 2509
defined, 1421
diagnosis of, 1431-1439, *1432-1439*, 2509
echocardiographic identification of, 1433-1438, *1436-1439*
incomplete. *See* Vascular sling
pathology of, 1430-1431
radiographic findings in, 707, 1431-1433, *1432-1435*
symptoms and signs of, 1431, 2509
with anomalous right subclavian artery, 1440, 2509
Vascular sling, 2509
defined, 1421
diagnosis of, 1445-1446, *1446*
pathology of, 1431
radiographic findings in, 707
Vascular stent(s), 994, *2201*, 2201
for pulmonary vein stenosis, 1169
Vasculitis
immune complex
in infective endocarditis, *2422*, 2422
Vasoactive amine(s)
effects on pulmonary circulation, 374t, 376
Vasoactive intestinal peptide (VIP)
pulmonary, 362
Vasoactive peptide(s)
effects on pulmonary circulation, 374t, 376-377
Vasoconstriction
hypoxic pulmonary, 369-370
Vasoconstrictor index, 333
Vasodilation
pulmonary vascular endothelium's role in, 366
Vasodilator(s), 2549t. *See also* particular drugs
for afterload manipulation
clinical applications of, 2091-2096
experiences with, in children, 2089t
mechanisms of action of, 2087-2088
pharmacology of, 2088t, 2088-2090
in congestive heart failure management, 2018-2019, 2020t
in cor pulmonale management, 2505
in myocardial infarction management, 1717
in persistent pulmonary hypertension management in neonate, 2486
in pulmonary vascular disease management, 2002-2003
in rheumatic heart disease management, 1521
intra-arterial injection of
in upper extremity angiography, 988
pharmacology of, 2088t, 2088-2090
in hepatic, gastrointestinal or nutritional disorders, 2366-2367
Vasopressin. *See* Antidiuretic hormone
Vasotec. *See* Enalapril
VATER association, 678, 2411, 2430t
congenital heart disease in, 678t
orthopedic problems in, 2457
renal anomalies in, 2430t
V_{cf}
as contractility index, *226-227*, 226-227
Vector
cardiac, *501*, 501
planes of, 501-502, *508*
defined, 619
lead, 502
Vectorcardiography, *508-509*, 508-509
Vecuronium, 2295t
Vegetation(s)
in infective endocarditis
prognosis and, 1565-1566
nonbacterial thrombotic
in infective endocarditis pathogenesis, 1562-1563
Veiling glare, 638
Vein(s). *See also* particular veins
histologic features of, 112
systemic
anomalies of. *See under* Systemic venous return
balloon dilation of, 2197-2198
development of, 98-103, *99*, *101*
echocardiographic assessment of, 774-775, *775*
Vein of Galen aneurysm, 1474
Vein of Marshall
development of, 100
Velocardiofacial syndrome, 2402-2403
Velometer
intravascular
blood flow measurement using, 496-497
Vena(e) cava(e). *See also* Inferior vena cava; Superior vena cava
anatomy of, 111-112
histologic features of, 112
Venous baffle. *See* Atrial baffle procedure(s)
Venous cannulation
for cardiopulmonary bypass, 2301
for intraoperative infusion and monitoring, 2296
Venous hum, 1922t, *1926*, 1926
in pregnancy, 2376
in total anomalous pulmonary venous connection, 1159
patent ductus arteriosus vs., 1064
Venous return
anomalous pulmonary. *See* Anomalous pulmonary venous connection(s); Total anomalous pulmonary venous connection
systemic. *See* Systemic venous return
Venous switch operation. *See* Atrial baffle procedure(s)
Venous thrombosis. *See* Thrombosis
Venous valve(s), 112
origin of, 84, 85
Vent
in cardiopulmonary bypass, 2301, *2302*
Ventilation. *See also* Respiration
changes in
with altitude, 442
collateral, 350
efficiency of, 432
frequency of
in response to exercise, 431
mask-and-bag
for asphyxiated neonate, 2478
maximum voluntary, 431
mechanical
for neonate, 2483
in pulmonary vascular disease patient, 2004
postoperative, 2253-2254
weaning from, 2254
mechanics of, 350-353, 354
during sleep, 354
minute
in response to exercise, 431
oxygen cost of
with pulmonary congestion, 674

work of, *355,* 355
Ventilation/perfusion matching, 356-357
effects of mismatch of
in exercise, 432
Ventricle(s). *See also* Left ventricle; Right ventricle
common-inlet
echocardiographic assessment of, *770,* 770, 771
double-inlet. *See* Single ventricle
double-outlet, 1213-1232. *See also* Double-outlet right ventricle
left, 1213, 1230
embryonic, 80-81
hypoplastic
computed tomography assessment of, *902,* 903
myocardial infarction due to, 1686
in fetus
echocardiographic assessment of, 808, *810*
size of, 819, *820*
isomyosins of, 218
morphology of
echocardiographic assessment of, 771-772
in fetus, 808, *810*
position of
electrocardiographic determination of, 724-726, *725-728*
primitive, 80-81
single. *See* Single ventricle
single-inlet
echocardiographic assessment of, *770,* 770, 771
single-outlet
echocardiographic assessment of, 772
Ventricular aneurysm. *See under* Aneurysm(s)
Ventricular arrhythmia(s), 1864-1904. *See also* particular arrhythmias
acute
clinical situations associated with, 1881-1883
after congenital heart defect repair, 1894-1896
surgical treatment of, 2181
chronic
clinical situations associated with, 1883-1896
in children and young adults, 1885-1888
in infants, 1884-1885
criteria for drug treatment of, 1896
electrophysiology studies of, 1879-1881, *1882-1883*
exercise electrocardiography in assessment of, 1739-1740, *1740,* 1740t
sudden death and, *1915,* 1915
treatment of, 1896-1900
surgical, 1899-1900
with cardiomyopathy, 1892-1894
with unoperated congenital heart disease, 1891-1892
Ventricular bigeminy, 1872-1874, *1873-1874, 1956*
Ventricular compliance. *See under* Compliance
Ventricular extrasystole(s). *See* Premature ventricular contraction(s)
Ventricular fibrillation, 1900-1901
cardiac arrest due to
alpha-adrenergic drugs for, 412-413
calcium for, 418
causes of, in children, 418
epinephrine for, 412-413
sodium bicarbonate for, 415-416
clinical situations and prognosis in, 1900
digoxin-induced
in Wolff-Parkinson-White syndrome, 1860-1861
electric current threshold for, 549-550
electrocardiographic characteristics of, 1900, *1901*
syncope due to, 1937
treatment of, 421, 1900-1901, 2171. *See also* Defibrillation
with myocardial infarction, 1715
management of, 1718
Ventricular function
abnormalities of
after surgery for transposition of the great arteries, 2039-2040
assessment of
during exercise testing, 832
echocardiographic, 780, *781*
in fetus, 820
diastolic
Doppler assessment of, 799-800, *800*
Ventricular hypertrophy. *See also* Cardiac hypertrophy
bilateral
electrocardiographic findings in, 731, *732*
left
after coarctation repair, 2032-2033
"by voltage criteria", 731
electrocardiographic findings in, *730,* 730-731
left bundle branch block with, 1789, *1791*
myocardial infarction vs., 1714
nuclear magnetic resonance imaging in, 863
myocardial perfusion imaging in, 845
nuclear magnetic resonance imaging in, 863-864
relative coronary insufficiency with myocardial infarction due to, 1686
right
body surface map findings in, 519
electrocardiographic findings in, *728-730,* 728-730
myocardial infarction vs., 1714
nuclear magnetic resonance imaging in, 863-864
Ventricular inversion, 1233-1245
atrioventricular valve abnormalities with, 1237
cardiac catheterization in, 1243
clinical features of, 1241-1242
conduction abnormalities with, 1239
defined, *725,* 1233-1234, *1234,* 1280-1281
dextrocardia with, 1239
differential diagnosis of, 1242-1243
echocardiographic assessment of, *770,* 770
electrocardiographic findings in, 726, *728*
myocardial infarction vs., 1714
embryology of, 1234-1236, *1235-1236*
heart block in, 1239, 1243
hemodynamics and physiology of, 1241
incidence of, 1234
isolated, 1179
management of, 1243-1244
normally connected great arteries with, 1236, *1237*
pulmonary stenosis with, 1237
transposition of the great arteries with, 1236, *1238. See also* Transposition of the great arteries, "corrected"
coronary arteries in, 1240-1241
embryology of, 1236
ventricular septal defect with, 1236-1237
Ventricular output
fetal
left vs. right, 283-284
Ventricular premature contraction(s). *See* Premature ventricular contraction(s)
Ventricular pressure. *See also* Left ventricular pressure; Pressure-volume loop(s); Right ventricular pressure
end-diastolic
as measure of preload, 233
end-diastolic volume and, 232, *233*
right-to-left ratio
prediction of, in tetralogy of Fallot management, 1093
Ventricular rhythm
accelerated, 1876, *1879,* 1887
Ventricular septal defect, 1002-1022
acquired conditions resulting from, 1003, 1005
acute
with myocardial infarction, *1709,* 1716
anatomy of, 1003-1005, *1004*
angiographic assessment of, 957t, 1013, *1013-1014*
aortic regurgitation with patent ductus arteriosus vs., 1065
atrioventricular canal defect with, 1038
echocardiographic examination of, 1044
atrioventricular canal type, 1003
atrioventricular conduction tissue and, 1004-1005
cardiac catheterization in, 1012-1013, *1013-1014*
classification of, 1003-1004, *1004*
clinical manifestations of, 1007-1008
computed tomography assessment of, *901-902,* 903
defined, 1002-1003
digital subtraction angiography in, *910*
disturbed flow in ventricular outflow tract with Doppler assessment of, 789, *791*
double-outlet right ventricle with, 1216-1217
clinical presentation of, 1219
physiology of, 1217, 1218
surgery for, 1229, *1230*
doubly-committed
in double-outlet right ventricle, 1216
doubly-committed subarterial, 1004
aortic regurgitation with, 1005
tetralogy of Fallot vs., 1076
echocardiographic findings in, 773, *774, 1010-1011,* 1010-1012
in fetus, 810, *811-812*
electrocardiographic features of, 1008-1009
embryology of, 1005
endocarditis and, 1017
history of, 1002
incidence and prevalence of, 1003
infracristal, 1003
insurability and, 1017
interrupted aortic arch with, 1374, *1375*
malalignment
in tricuspid atresia, 1119
management of. *See also* Ventricular septal defect, surgery for
guidelines for, 1017, 1018t
medical, 1014-1015, 1016
presenting at 2-18 weeks, 1967
presenting at 4-12 months, 1968
membranous. *See* Ventricular septal defect, perimembranous
moderate-size
clinical manifestations of, 1007-1008
murmur in, 687, 688, 1007, 1008
Still's murmur vs., 1923
muscular, 1004

Ventricular septal defect, muscular *(cont.)*
in tetralogy of Fallot, 1076
in tricuspid atresia, 1119
natural history and clinical course of, 1013-1014, 1014t
noncommitted
in double-outlet right ventricle, 1216
nuclear magnetic resonance imaging in, *858,* 858, 1012
patent ductus arteriosus vs., 1064
patent ductus arteriosus with, 1067
perimembranous, 1003-1004
aneurysm of ventricular septum with, 1005
in tetralogy of Fallot, 1076
in tricuspid atresia, 1119
persistent
after tetralogy of Fallot repair, 1096, 2036
physiology of, 1005-1007
pregnancy with, 1017, 2379
pulmonary atresia with
angiographic assessment of, 958t-959t
echocardiographic assessment of, 777
patent ductus arteriosus vs., 1066
pulmonary infundibular stenosis vs., 1407
pulmonary valve stenosis vs., 1396
radiographic findings in, 697, *699-700,* 1009, *1009-1010*
radionuclide studies of, 1012
recurrence risk for, 176t
restrictive
in double-outlet right ventricle, 1216-1217, *1217,* 1223
in tetralogy of Fallot, 1076
small
clinical manifestations of, 1007
spontaneous closure of, 1014
subaortic
in double-outlet right ventricle, 1216, 1218, 1219, 1229
subpulmonic
in double-outlet right ventricle, 1216, 1218, 1219, 1229, *1230*
supracristal, 1003, 1004
surgery for, 1015-1017, 2029-2030
complications of, 2030-2031
decisions and techniques for, 2212-2213
indications for, 1015-1016, 1016t
long-term results of, 1017
patient selection for, 2031
postoperative management, 1016
radionuclide evaluation of left ventricular function after, 842
residua of, 2030
right bundle branch block after, 1788, 1789
sequelae of, 2030
tetralogy of Fallot with, *1076,* 1076
persistent defect after repair, 1096, 2036
repair of, 1092-1093
transposition of the great arteries with, *1177,* 1177-1178
traumatic, 2537, 2538
tricuspid atresia with, 1119
Type I, 1003
Type II, 1003
Type III, 1003
Type IV, 1003
vasodilators for congestive heart failure in, 2093-2094, *2094*
ventricular inversion with, 1236-1237
hemodynamics and physiology of, 1241
with high pulmonary vascular resistance
clinical manifestations of, 1008
complications of repair of, 2263-2264
medical therapy for, 1015
Ventricular septum
anatomy of, 119, *120*
aneurysm of. *See* Aneurysm(s), ventricular
apical trabecular, 1003
echocardiographic assessment of, 773, *774*
in fetus, 810, *811-812*
formation of, 86-88, *89-91*
in atrioventricular canal defects, 1038
infundibular. *See* Ventricular septum, outlet
inlet, 1003
formation of, 86-87, *89*
membranous, 1003
outlet, 1003
formation of, 87-88, *90-91*
in double-outlet right ventricle, *1214,* 1214
perforation of
after myocardial infarction, 2283
regions of, 1003, *1004*
Swiss cheese, 1004
Ventricular tachycardia. *See also* Ventricular fibrillation
acute clinical situations associated with, 1881-1883
bidirectional, 1875, *1878*
in digitalis toxicity, *750,* 750
chronic
in infants, 1884-1885
differential diagnosis of, 1874-1875, 2546t
during pregnancy, 2382
electrocardiographic characteristics of, 1874-1876, *1875-1879*
electrophysiology studies of, 1749, 1879-1881, *1882-1883*
exercise-related, 1740, 1888
fetal, 1884
in otherwise normal heart, 1887-1888
in unoperated congenital heart disease, 1891-1892
in unoperated mitral valve prolapse, 1891
incessant, in infants
with myocardial tumor or hamartoma, 1640-1641, *1641,* 1653, 1884-1885, *1885-1887,* 2179-2181, *2180,* 2181t
management of
acute, 1897-1898
cardioversion in, 2171
chronic, 1898-1900
emergency, 2547t
surgical, 2179-2181, *2180*
with myocardial infarction, 1718
monomorphic
defined, 1881
noninvasive evaluation of, 1876-1879
nonsustained
defined, 1881
paroxysmal
in infants, 1884
polymorphic
defined, 1881
postoperative, 2258
preceding cardiac arrest
age and, 420-421
sudden death and, *1915,* 1915
supraventricular tachycardia vs., 1820, *1821*
sustained
defined, 1881
syncope due to, 1937, *1940*
torsades-de-pointes, 1875, *1879*
acute management of, 1897
in quinidine toxicity, 751, *752*
with myocardial infarction, 1715
management of, 1718
Ventricular trigeminy, 1872-1874, *1873*
Ventricular tumor(s)
tachycardia and syncope due to, 1937, *1940*
ventricular arrhythmias with, 1892, 1899-1900
in infants, 1640-1641, *1641,* 1653, 1884-1885, *1885-1887,* 2179-2181, *2180,* 2181t
Ventricular volume
as measure of preload, 232, *233*
calculation of, from cine-angiography, 496
Ventricular wall motion. *See* Wall motion
Ventricular wall stress. *See* Wall stress
Ventriculoarterial connection
echocardiographic assessment of, 771, *771-772, 779*
in fetus, 810, *813*
Ventriculoatrial shunt
for hydrocephalus
infections involving, 2463
Ventriculography. *See* Angiocardiography
Ventriculoinfundibular fold, 115-116, *116*
in double-outlet right ventricle, *1214,* 1214
Ventriculomyotomy. *See also* Myectomy
for hypertrophic cardiomyopathy
ventricular arrhythmias after, 1896
Ventriculoperitoneal shunt
for hydrocephalus
infections involving, 2463
Ventriculoradial dysplasia, 678t, 678
Ventriculotomy
right bundle branch block after, 1788
sequelae of, 2030
Verapamil, 2127t, 2133, 2551t
dosage adjustment for renal insufficiency, 2440t
drug interactions with, 2133
effects of
on abnormal automatic rhythms, 314
on electrocardiogram, 751
on pulmonary circulation, 374t, 378-379
for atrial flutter, 1857
for fetal tachycardia, 1908-1910
for hypertrophic cardiomyopathy, 1633
for myocardial protection, 271
for supraventricular tachycardia, 1822, 1825
for ventricular arrhythmias, 1899
for ventricular fibrillation, 1901
in cardiopulmonary resuscitation, 418
mechanism of action of, 305
pharmacokinetics of, 2133, 2364t
pharmacology of
in hepatic, gastrointestinal or nutritional disorders, 2366
problems with
in Wolff-Parkinson-White syndrome, 1914
side effects of, 2133
sinus node dysfunction and, 1775
use of, during pregnancy, 2385, 2386t
ventricular tachycardia and, 1897-1898
Vertebral artery(-ies)
formation of, 94
Vertical vein
anomalous
in partial anomalous pulmonary venous connection, 1149
in total anomalous pulmonary venous connection, 1154
Vertigo
syncope due to, 1940
Very-low-density lipoprotein. *See under* Lipoprotein(s)
Victorica and Gessner formula, 938, *939*
Vidarabine (adenine arabinoside), 2061

Vidicon tube(s), 555, 639
Vincristine
cardiotoxicity of, 2341
Virus(es). *See also* particular diseases
congenital infections with
cutaneous manifestations of, 2421
oncogenic, 30
Visceral situs. *See* Situs
Vistaril. *See* Hydroxyzine
Vital capacity, 353
Vitamin(s). *See also* particular vitamins
supplemental, 2354
Vitamin B_1. *See* Thiamine deficiency
Vitamin C
in iron chelation therapy, 2333
Vitamin D
supravalvular aortic stenosis and, 1343
Vitamin D-endocrine system, 463
Vitamin K
neonatal supplementation with, 2354
Vitelline vein(s), 98-99, *100*
V_{max}, 235, *236*
as contractility index, 225-226
VNTR (variable number of tandem repeat marker), 23
Voltage
activation, *296*, 296
defined, 2140
Voltage clamp experiment(s), 302
Volume of distribution
apparent, 469
Volume overload
blood pool imaging for assessment of, 842
chronic
effects on liver, 2359-2360
Von Recklinghausen disease. *See* Neurofibromatosis
Von Willebrand factor
endothelial synthesis of, 486
in pulmonary hypertension, 372
Von Willebrand's disease
mitral valve prolapse in, 2343
Voxel(s)
defined, 619, 630, 852
VP-16
cardiotoxicity of, 2341
Vulnerable period, 1871

Walker-Murdock sign, 2398
Wall motion
assessment of
by equilibrium blood pool imaging, 839
by first-pass blood pool imaging, 841
Wall stress, 232
afterload estimation from, 224
estimation of, 224, 251-252
increased
hypertrophy as compensation for, 252
instantaneous
afterload and, 235
internal cardiac work and, 251-252
myocardial oxygen consumption and, 252
compensatory effect of cardiac hypertrophy on, 246
Wandering pacemaker, 1954
Warfarin (Coumadin), 2080, 2553t
drug interactions with, 2080t
for pulmonary embolism, 2510
in idiopathic dilated cardiomyopathy management, 1624
in mitral prosthesis management, 1314
pharmacology of, 2364t
in hepatic, gastrointestinal or nutritional disorders, 2367
use of, during pregnancy, 2080, 2382
Warfarin embryopathy syndrome, 2382
Warming device(s)
for cardiac catheterization laboratory, 948-949
for neonate, 2481
Wasting, 2355
Water. *See also* Fluid(s)
excretion of
quantitation of, 456
renal transport of
regulation of, *2100*
Water loss
in neonate, 2482
Water-hammer pulse. *See under* Pulse
Watershed infarct(s)
due to cardiac surgery, 2313
Waterston-Cooley shunt, 2211
for single ventricle, 1268-1270
for tetralogy of Fallot, 1091-1092
sequelae of corrective surgery after, 2037-2038
for tricuspid atresia
drawbacks of, 1123, *1124*
nuclear magnetic resonance imaging of, 860
Watson, James, 4-5
Weight
birth
altitude and, 446
congenital heart disease and, 677
dosage schedules based on
multipliers for adult dose, 837t
nutritional status and, 2355
Weightlessness
birth, growth and development in, *438*, 438-439, 439t
effects of, 435-437, *436-437*, 437t
Wenckebach block. *See under* Atrioventricular block, second-degree
Werner's syndrome
atherosclerosis in, 1993
Wet lung syndrome. *See* Transient tachypnea of newborn
Wheezing
in myocardial infarction
management of, 1717
White, Paul Dudley, 1988, 1989
Wide QRS tachycardia
differential diagnosis of, 1820, *1821*
Wilcoxon method, 653
Williams syndrome, 980-981, 1344, 2407-2409, *2408*, 2430t
endocrine abnormalities in, 2498t
molecular basis of, 55
myocardial infarction in, 1712-1713
pulmonary artery stenosis in, 1409, *1412*
renal anomalies in, 2430t
supravalvular aortic stenosis and, 677t, 1343
Williams-Beuren syndrome. *See* Williams syndrome
Wilms' tumor, 988, *989*
involvement of great vessels or heart in, 2338, *2339*
Wilson, Frank
on faulty reading of electrocardiograms, 713
Wilson's central terminal, 504-506
Wilson's disease, 1674
Window-level setting, 630, *631*
Window-width setting, 630-631, *631*
Wobble hypothesis, 5-6
Wolff-Parkinson-White syndrome, 738-740, *739-740*
atrial fibrillation in, 1860-1861
atrial flutter in, 1853-1854
blood pool imaging in assessment of, 843
clinical applications of body surface mapping in, 519-520, *520*
concealed. *See* Kent bundle, concealed
digoxin use in, 1824, 1860-1861
electrocardiographic findings in
myocardial infarction vs., 1714
electrophysiologic studies in, *1748-1749*, 1749
exercise electrocardiography in assessment of, 1739
in Ebstein's anomaly, 1137, *1138*
inheritance patterns of, 55
intermittent, 1838
premature ventricular contractions vs., 1869
supraventricular tachycardia in, 1813, 1818t, 1834t, 1838, *1839*, 1839-1841
digoxin in management of, 1824
electrocardiographic characteristics of, 1835t, 1846t
electrophysiologic diagnosis of, 1830-1831, *1831-1832*, 1835t
inheritance pattern of, 55
sudden death and, *1914*, 1914
surgery for, 2174-2176, *2175-2178*, 2176t
treatment of, 1840-1841
ventricular tachycardia vs., 1881
syncope in, 1932, *1934-1935*
ventricular fibrillation in, 1900, 1901
Wolf-Hirschhorn syndrome, *184*, 184
Wolman disease, 1662
Wood unit(s), 932-933
Word processing program(s), 662
Work
cardiac
carbohydrate metabolism in response to, 194
lipid metabolism in response to, 195
myocardial oxygen consumption for, *251-252*, 251-253
of breathing, *355*, 355
Workers' Compensation, 2529

Xanthine oxidase
in free radical generation
in postischemic dysfunction, 275
Xenon
radionuclide-labeled
blood flow measurement using, 496
Xiphoid
hypersensitive, 1948
X-linked dominant inheritance, 174
X-linked recessive inheritance, 174
X-ray(s) (roentgen ray), 560
image creation by, 628
production of, 552, 553
X-ray beam
hardening of, 637-638
X-ray generator
for digital subtraction angiography system, 636
X-ray imaging system(s)
beam energy of, *629*, 629
image quality in, 628-630, *629-630*
X-ray tube(s), 553-554, *629*
for digital subtraction angiography system, 636

Yersinia enterocolitica infection
Lyme disease vs., 1538

Yersinia pseudotuberculosis infection
  Kawasaki disease and, 1549-1552
  Kawasaki disease vs., 1549

Z band(s), 130
Z filament(s), 212
Z line, 212
Zaroxolyn. *See* Metolazone
Zellweger syndrome, 2430t
Zero crossing circuit, 539
Zero-flow pressure, 256
Zeumatography
  rotating frame, 613
Zinacef. *See* Cefuroxime
Zofenopril
  pharmacology of
    in hepatic, gastrointestinal or nutritional disorders, 2367

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